Proposal to include drugs for treating fungal infections in children including opportunistic and inter-current fungal infections in those infected with HIV

1. Summary statement

Children can get infected with a variety of fungi. The most common fungal infections in children affect skin and mucus membranes. Systemic fungal infections are important causes of mortality in the immunosuppressed including children. Treatment options for these infections are not fully satisfactory as yet. With the wide spread use of HAART, frequencies of opportunistic infections including fungal infections have come down. However, these infections continue to occur. Added to this is the fact that HAART is not universally accessible to all infected, especially in the developing countries. Although candidiasis is the most common fungal infection in the HIV infected, other systemic and superficial fungal infections also occur with varying frequencies.

The variety of drugs available for the treatment of fungal infections has increased in the recent years. The choice of drugs for a patient will depend on the infecting species, site and severity of infection, patient characteristics and also cost. To allow choices, the essential drug list needs to have a number of different antifungals for systemic and topical therapy. Including these drugs will help in providing adequate care to HIV infected and other children. Most of these drugs are already part of treatment guidelines of the WHO and other agencies, for the HIV infected children.

Several of these drugs are included in the model WHO essential drug list or the complimentary list. This application is therefore for the inclusion of systemic and topical antifungal drugs for use in children. Although many of these drugs are recommended and used in children, data on efficacy and safety in children, especially in the case of newer drugs, is scanty. Therefore some of the recommendations are based on experience in adults. Although *Pneumocystis jiroveci* is a fungus, drugs for treating this infection is not included in this application.

2. Name of the focal point in WHO submitting or supporting application

3. Names of organisations consulted and or supporting the application

4. International non – propriety name (INN generic name) of the medicines

5. Information supporting public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Fungi are important causes of serious and life threatening opportunistic infections in the immunosuppressed, including children [1-3]. Although there is substantial reduction in the burden of opportunistic infections in those children receiving HAART, the relative prevalence of AIDS defining illnesses remain similar to pre HAART era [4, 5]. Also, there are large numbers of children in developing countries for whom HAART is still not accessible. Candida spp are also responsible for significant numbers of nosocomial infections [6]. The incidence of fungal infections is increasing in children with malignancies on chemotherapy and after transplantations[7]. Mortality in patients with deep fungal infections is still in the range of 50 to 95% [1]. Therefore, there is a need to improve diagnosis, management and prevention of such infections. Choice of therapy and or prophylaxis will depend on the infecting fungus, site of infection, severity of infection, immune status of the patient, presence of other complications and cost. Rational use of antifungal therapy will help in reducing mortality due to these infections and in improving quality of life.

Oral [8, 9], pharyngeal, oesophageal, tracheo-bronchial and disseminated forms of candidiasis are the most common fungal infections in the HIV infected. Oral thrush and diaper dermatitis occur among 50%--85% of HIV-infected children [4]. Candidiasis is a marker of HIV disease and is utilised for the clinical categorisation of HIV related illness in children [10]. Candida oesophagitis is reported as the AIDS-defining condition in approximately 12%--16% of children aged <13 years in the United States, and is seen in the HAART era among children who are not responding to therapy[4]. Therefore interventions to prevent and treat candidiasis are important aspects of management of children with HIV infection. Candidemia is usually associated with central venous catheters and occurs in about 12 % of children with HIV on long term central lines. Mortality attributable to candidemia is 38%[6]. Overall, *Candida albicans* is the most common species responsible. However recent data from different parts of the world show that infections due to non albicans candida species like *C glabrata, C krusei and C tropicalis* are on the increase [6]. About 50% of candidemia in HIV infected children are reportedly due to 'non albicans' candida. Several of these species show varying degrees of resistance to Fluconazole [4, 11].

Although clinical manifestations of oro-pharyngeal candidiasis can be varied, therapy can be initiated based on clinical diagnosis [12, 13]. While early uncomplicated infections are treated with topical applications of drugs like nystatin, clotrimazole or miconazole, systemic therapy with oral azoles or amphotericin B may be required depending on severity of infection and susceptibility of infecting strain[4]. WHO also recommends these drugs for candidiasis in children [4, 12-14]. About 50% of oro- pharyngeal candidiasis refractory to Fluconazole will respond to itraconazole [4]. For oesophageal infections, systemic treatment with Fluconazole or itraconazole has to be started based on symptoms [4]. For severe invasive infections amphotericin B is still used [4].

Another life threatening opportunistic infection in HIV infection is cryptococcosis[3, 15]. It occurs in about 1% of HIV infected children, primarily in those aged 6 -12 yrs[4]. Although many sites like skin, respiratory system etc can be affected by this fungus, meningo-encephalitis is the most common manifestation. This infection is an important cause of mortality in the HIV infected. Mortality can be as high as 44% even after treatment in tertiary level hospitals in developing countries[16]. Microscopic examination of India-ink wet mounts of CSF is a reliable method for specifically diagnosing this condition. Antigen detection and culture methods are also very useful. Cryptococcosis is fatal if untreated. There is not much evidence base for the choice of therapy in children. A combination of amphotericin B and flucytosine is recommended for induction by the IDSA [17]. This is followed by a maintenance therapy with fluconazole [4, 12, 13]. Life long prophylaxis may be required to prevent relapse. However, in many developing countries where availability of drugs and cost are important issues, monotherapy with Fluconazole is often used [18]. Children with this condition are better treated in hospitals with facilities to manage disease related and drug related complications.

Rarer opportunistic infections include histoplasmosis, coccidiodomycosis, penicilliosis, aspergillosis, zygomycocis etc[3, 15]. The incidence of histoplasmosis in HIV infected children in the US is 0.4% and is 2.7% to 3.8% in Argentina, Brazil and Mexico. Diagnoses of these infections require facility to culture and fungi can take several weeks to grow. Immunological and molecular methods though described for some, are not widely available. These infections are therefore difficult to diagnose at primary care facilities but are fatal without treatment. The optimum treatment has not been evaluated in a controlled manner among children with HIV. Mortality can be high even with therapy. The drugs currently in use for these conditions include fluconazole, itraconazole and Amphotericin B [4, 12]. Treatment with these drugs can be associated with drug related complications. These infections are usually managed in referral hospitals.

Fungal skin infections are common in children and can be associated with HIV clinical disease [13],. Infections due to dermatophytes are commonly referred to as ringworm infection and tinea and can affect hair and nails also in addition to skin. This infection can be diagnosed based on clinical presentation and microscopy of potassium hydroxide mounts of skin scrapings, nail clippings or hair. Treatment is mostly topical with Whitfield's ointment or antifungal creams like miconazole, clotrimazole or terbinafine[12, 19]. Oral therapy with griseofulvin, azoles or terbinafine may be required in certain infections [13, 19]. Another fungal infection that may require therapy in children is vaginal candidiasis.

Therefore, to manage fungal infections in children rationally and effectively several systemic and topical antifungal drugs have to be included in the list of essential drugs. While some of these, especially the formulations for topical use can be used safely in primary health facilities, others may be reserved for use in hospitals with facilities to monitor for and manage complications related to the drug and also the disease. Since some of these drugs have serious adverse events and several drug interactions, the physician should have adequate knowledge on the use of these drugs. Some details of individual drugs are described in the following sections.

Antifungal drugs	Rationale
Systemic Fluconazole	Many indications, on treatment guidelines for children
Itraconazole	Alternative to fluconazole for candidiasis especially in HIV infected, on treatment guidelines for children
Amphotericin B	Drug of choice for several invasive infections, part of guidelines for children
Flucytosine	For induction therapy of cryptococcal infections, part of guidelines for children
Caspofungin	Alternative to amphotericin B for severe and resistant candidiasis, less toxic, part of guidelines
Griseofulvin	Dermatophyte infections requiring systemic therapy, part of guidelines
Terbinafine	Clinically better than griseofulvin for dermatophyte infections, shorter duration therapy, Both topical and oral
Potassium iodide	Therapy of sporotrichosis
Topical Terbinafine	For dermatophyte infections
Clotrimazole	For superficial candida infections, part of guidelines for children
Nystatin	Alternative drug for superficial candida infection, part of guidelines for children
Miconazole nitrate	Alternative for superficial candida infection
Whitfield's ointment	Dermatophyte infections
Gentian violet	Topical therapy of mucosal and cutaneous candidiasis, as an inexpensive alternative

Fluconazole

Trials summarized in tables

De Wit 1989
De Wit 1993
De wit 1998
Graybill 1998
Hernandez 1994
Just Nubling 1991
Leen 1990
Marriott, 1993
Pagani, 2002
Phillips, 1998
Pons, 1993
Pons,1997
Redding, 1992
Revanker, 1998
Schuman, 1997
Stevens, 1991
Dreissen,1996
Cabrera, 2002
Kaufman, 2001
Kicklighter 2001
Chetchotisakd, 2004
Powderely,1995
Kontoyiannis D P, 2001
Girois, SB 2005
Crawford, F 2002
Chotmongkol V,2005
Brouwer AE, 2004
Mootsikapun P, 2003
Villanueva A, 2002
Saag, MS 1999

1. Formulation proposed for inclusion

For oral use

Tablets-capsules - 100mg/ Tab-cap or 50mg/ Tab-cap

50 mg/ Tab-cap is on the WHO essential drug list

Suspension – 50mg/ml – also on WHO essential drug list

For injection – 2mg/ml glass ampoule

The drug is almost fully absorbed from GIT and so indications for parenteral therapy are very limited. Cost is much higher for parenteral therapy. Hence the application is for including oral formulations only – preferably tab-cap since doses will be more accurate with this formulation than with suspension.

2. International availability (sources)

100mg/tab-cap - Missions and JMS

50 mg/tab-cap – IDA, MEDS

50mg/5ml oral suspension– no supplier listed- there are several manufacturers – (Ranbaxy, Roxane, Pfizer)

2mg/ml injection – Diflucan – Pfizer

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug.

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

References for general information including pharmacokinetics- Goodman and Gilman [20], product information form Pfizer [21] and British National Formulary (BNF) for children.

Fluconazole is a synthetic triazole anti fungal agent which selectively inhibits the fungal cytochrome P 450 enzyme, C-14 alpha sterol demethylase. There is very little action on human sterol synthesis. The drug is almost fully absorbed after oral administration and so pharmacokinetic properties are similar following oral and intravenous administration. After oral administration peak plasma concentrations are achieved in one to two hours and elimination half life is about 30hrs. Steady state concentrations are reached within 5- 10 days following single daily oral doses. A loading dose of twice the usual daily dose helps in achieving steady state within two days. In children the elimination half life is about 15 -25 hrs. In premature neonates, the half life is about 88hrs and decreases to about 55 hrs in two weeks. The drug reaches all body fluids including CSF and the concentrations in these fluids are almost similar to that found in plasma. The drug is excreted primarily through the kidneys and about 80% is excreted unchanged. Renal impairment affects excretion of the drug and so dosage has to be adjusted.

The azole drugs can have substantial interactions with other drugs undergoing hepatic metabolism. This can result in decreased plasma concentration of the azole, or development of unexpected toxicity from the coadministered drug because of increased plasma concentrations secondary to azole-induced alterations in hepatic metabolism. For example, rifampin can reduce plasma fluconazole levels. Fluconazole further increases prothrombin time when used with warfarin. Fluconazole can cause increase in phenytoin, cyclosporine, zidovudine, theophylline and terfenadine levels. There is higher chance of hypoglycaemia with oral hypoglycemics. This has implications on treatment decisions.

Fluconazole has in vitro activity against several candida species and cryptococci.[22-24]. However some candida species like *C krusei* are resistant to fluconazole and others show varying degrees of susceptibility [6]. It is estimated that the annual incidence of fluconazole resistant, AIDS related oropharyngeal candidiasis is about 5%. In addition, fluconazole resistance can develop in *C albicans* and other species, during treatment, due to a variety of machanisms. The drug has activity against dermatophytes, *Histoplasma capsulatum* and *Coccidiodis immitis*. There is no activity against mucor group of organisms and the activity against Sporothrix and Aspergillus species is intermediate. It has been found useful for treating fungal keratitis due to filamentous fungi[25]

Indications for use

Candidiasis

Treatment
Oral and oro-pharyngeal candidiasis when systemic therapy is indicated
Oesophageal candidiasis
Vulvo-vaginal candidiasis
For invasive forms of candidiasis, amphotericin B is the drug of choice. However, Fluconazole can be used as an alternative in normal children if infection is due to susceptible species. In the immunocompromised and in severe neutropenia the drug may not be effective. But may be used as maintenance therapy after initial therapy with amphotericin B
Emperical therapy of fever in neutropenics not responding to antibacterial therapy and not on Fluconazole prophylaxis

Candiduria when treatment is indicated, fluconazole is an option. Clinical decision on when to treat a patient with candiduria can be difficult. Candiduria can be a manifestation of invasive candidiasis also.
Fluconazole is useful for treating disseminated cutaneous candidiasis in the new born. Amphotericin is the first choice[6]

Prophylaxis
Routine use of Fluconazole for primary prophylaxis in the immunocompromised patients including the HIV infected is not recommended due to the potential of developing infections with drug resistant candida. However, prophylaxis has been found useful in situations like bone marrow transplantation, very low CD4 counts in the HIV infected and in preterm very low birth weight infants.
Fluconazole is useful as secondary prophylaxis to prevent relapse of oropharyngeal and oesophageal candidiasis in the HIV infected.

Cryptococcal infections
For cryptococcal meningitis, oral fluconazole is used as consolidation therapy for 8 weeks, following initial induction therapy and clinical improvement with amphotericin B.
In addition, life long maintenance suppressive therapy, at lower doses may be required.

Other mycoses
Fluconazole is the drug of choice for coccidioidal meningitis
It is inferior to itraconazole for treating blastomycosis, histoplasmosis, sporotrichosis and dermatophyte infections. Not licensed for tinea infections in children (BNF C)

It is not useful for treating aspergillosis or mucormycoses

Therapy for mucosal candidiasis can be initiated on clinical grounds while diagnoses of invasive candidal and cryptococcal infections require laboratory support. Microscopic examination of India ink wet mount of CSF can be used to diagnose cryptococcal meningitis. However culture is more reliable for diagnosing invasive infections.
Susceptibility testing in candidiasis can help, but is not a must for initiating treatment.

Dosage
- Oral Fluconazole 3-6mg/kg as single daily dose. Doses up to 12mg/kg can be used for severe infections. For neonates, the drug is given every 48 - 72hrs during first two weeks of life (BNF C recommends every 72 hrs till second week and every 48hrs till fourth week) . A loading dose of double the usual dose is given on day one.
- Maintenance dose has to be adjusted based on renal clearance (21- 50ml/min – reduce by 50%, 11 – 20 ml/min – reduce by 75%). Loading dose can be the same.
- For oropharyngeal candidiasis the treatment is for 7-14 days, for oesophagitis and other serious mucosal infections for 14-30 days, for invasive candidiasis minimum of 4 weeks or 14 -21 days after resolution of signs and symptoms and negative repeated cultures [6]
- For vaginal candidiasis a single dose of 150 mg for 16 to 18yr olds.
- For cryptococcal meningitis, several weeks of treatment and life long prophylaxis
- Dosages for prophylaxis in the preterm infants and after bone marrow transplantation are similar to that of therapy (BNF C)

Interactions with co administered drugs have to be considered. Most children requiring fluconazole are likely to have other underlying disorders.

The patient has to be monitored for adverse reactions especially liver functions and skin manifestations
Fluconazole is recommended for children in the following guidelines [4, 6, 12, 13]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, exclusion of particular data)

Oral and oesophageal candidiasis
Another review analysing 19 trials on treatment and nine on prevention of oropharyngeal candidiasis in the HIV infected found that Fluconazole therapy resulted in more cures compared to nystatin but there was no difference in clinical cure between Fluconazole and itraconazole (2 RCTs; n=434; RR 1.05; 95% CI 0.94 to 1.16), ketocanazole(2 RCTs; n=83; RR 1.27; 95% CI 0.97 to 1.66) or clotrimazole (2 RCTs; n=358; RR 1.14; 95% CI 0.92 to 1.42). When compared with clotrimazole, both fluconazole (2 RCTs; n=358; RR 1.47; 95% CI 1..16 to 1.87) and itraconazole (1 RCT; n=123; RR 2.20; 95% CI 1.43 to3.39) showed better for mycological cure[26]. Fluconazole was found to be useful in preventing relapse as compared to no treatment or placebo[26]. There was no data on the usefulness of other drugs for prophylaxis. The studies included in this review are summarised in table1. There was only one study in children. Other studies in children also show that fluconazole is safe and effective in treating oropharyngeal candidiasis[27]

Candidemia
A meta analyses of trials using amphotericin B and Fluconazole for treating candidemia showed that amphotericin B and Fluconazole are equally effective in reducing overall and infection specific mortality and in bringing about microbiological cure in patients who are not severely immunocompromised and at low risk of death, irrespective of infecting species[28]. Details are summarised in table 3. Fluconazole is useful for treating candidemia and other invasive infections [29] in children and neonates as well[30, 31]. A Cochrane review for treatment of invasive fungal infections in preterm infants found only one eligible study and this showed fluconazole to be at least effective as amphotericin B[32]. Another review found that prophylactic use of fluconazole in very low birth weight infants may reduce mortality[33]. Studies in these two reviews are summarised in table 2

Cryptococcal infections
On reviewing the usefulness of primary prophylaxis for cryptococcal meningitis in adults with advanced HIV disease, it was found that Fluconazole decreased the incidence of cryptococcal meningitis, but did not significantly reduce mortality as compared to placebo[34]. Studies included in this review are summarised in table 3. Fluconazole is found useful in a few RCTS for maintenance therapy following therapy with amphotericin B and for secondary prophylaxis of cryptococcal meningitis [35, 36].

Other indications
It is found to be useful for prophylaxis in children undergoing bone marrow transplantation[37]. A recent RCT found that for treatment of tinea capitis in children, both fluconazole and griseofulvin had poor cure rates [38]. In a review analysing trials comparing

Fluconazole and amphotericin B there was no significant difference in mortality, invasive fungal infections or colonisation in neutropenic patients between treatments [39]

Some authors of meta analyses have commented that several studies used in he analyses are industry sponsored and the designs may be inherently biased. The data therefore may be insufficient to discredit older treatment modalities.

6. Summary of comparative evidence on safety

13% of 577 children in the US and Europe, included in phase 11/111 trials [21] had adverse reactions. Most common were vomiting, abdominal pain, nausea and diarrhoea. Treatment was stopped in 2.3% due to clinical adverse effects and in 1.4% due to lab abnormalities like elevated serum transaminases and alkaline phosphatase.

Data from adults show that about 21% of those HIV positive receiving therapy experience adverse effects [21]. Adverse events are lesser in the non HIV positive. Head ache is also common. Hepatobiliary adverse events, mainly transient elevations of liver enzymes were observed in a few patients. The magnitude of hepatobiliary involvement can vary and fatality due to hepatic failure is reported. Skin rashes can occur and severe forms like exfoliative disorders and Steven Johnsons are reported. Severe complications are more common in those with malignancies and AIDS and in those taking other medications. Alopecia which is reversible can occur. Other reported adverse events include seizures, neutropenia, agranulocytosis, and hypokalemia. Anaphylaxis is rare but reported. Complications like bacteremia were more with Fluconazole compared to amphotericin B[39]. Most patients included in the RCTS receive other drugs also.

One meta analyses found that Fluconazole has lesser significant adverse reactions compared to other antifungal drugs [40]. Details of this analysis are in table 3.

It is teratogenic in rats and so is a category C drug.

There are several drug interactions and includes interactions with anti retrovirals. Another important interaction with terfanidine increases cardiac toxicity.

7. Summary of available data on comparative cost

Median cost of 50mg/ tab-cap is US$ 0.1059/ cap and that of 100mg/tab-cap is 0.3537.
Oral suspension - buyer price – US$ 0.8931/ml
For parenteral use the buyer price is 0.2027/ml (2mg/ml)

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Fluconazole has many applications in reducing mortality and morbidity among children, especially in those with lower natural resistance to infections..
If the daily dose requirement is assumed to be 100mg, the 50 mg tab-cap will cost about US$ 0.2 and the 100mg tab-cap US$ 0. 35
Cost of oral suspension for the same dose will be US$ 1.7
For 100mg IV drug the cost will work out to about US$ 10
Acquisition costs are only one aspect of antifungal therapy. One has to consider other costs like hospitalisation, monitoring for adverse reactions etc

9. Summary of regulatory status

Oral and parenteral preparations are FDA approved for several indications and from several manufacturers.

10. Availability of pharmacopoeial standards

Listed in US pharmacopoeia and EU pharmacoepoeia.

11. Proposed text for WHO model formulary

Fluconazole 50mg tab-cap to betaken orally.

This antifungal drug has good activity against several species of Candida and *Cryptococcus neoformans*

Uses in children

Treatment

Oral and oro-pharyngeal candidiasis when systemic therapy is indicated

Oesophageal candidiasis

Vulvo-vaginal candidiasis

Mild to moderately severe forms of invasive candidiasis; as initial therapy in normal children and as maintenance therapy in the immunocompromised

Candiduria when treatment is indicated.

Disseminated cutaneous candidiasis in the new born if Amphotericin cannot be used

Emperical therapy of fever in neutropenics not responding to antibacterial therapy in cases not on fluconazole prophylaxis

Consolidation and maintenance therapy of cryptococcal infection

Coccidioidal meningitis

Prophylaxis

Routine primary prophylaxis is not recommended.

It may be of use in limited situations like bone marrow transplantation, very low CD4 counts in the HIV infected and in preterm low birth weight infants.

Secondary prophylaxis to prevent relapse of oropharyngeal and oesophageal candidiasis in the HIV infected.

Contraindications

Known hypersensitivity

CO administration of drugs that can cause serious interactions

Precautions

Interactions with co administered drugs have to be considered

The patient has to be monitored for adverse reactions especially liver functions and skin manifestations. Patients or care givers should be informed of adverse events.

Pregnancy category C

Dosage

3-6mg/kg as single daily dose. Doses up to 12mg/kg can be used for severe infections. For neonates, the drug is given every 48 - 72hrs during first four weeks of life. A loading dose of double the usual dose is given on day one.

Maintenance dose has to be adjusted based on renal clearance (21- 50ml/min – reduce by 50%, 11 – 20 ml/min – reduce by 75%). Loading dose can be the same.

For oropharyngeal candidiasis the treatment is for 7-14 days, for invasive candidiasis minimum of 4 weeks or 14 -21 days after resolution of signs and symptoms and negative repeated cultures and for vaginal candidiasis single dose.

For cryptococcal meningitis, several weeks of treatment and life long prophylaxis

Adverse reactions

Fluconazole is a relatively safe drug. Reported adverse events are
GIT related -vomiting, abdominal pain, nausea, dyspepsia and diarrhoea
Hepatobiliary - transient elevations of liver enzymes - magnitude can vary
Head ache
Skin - rashes and rarely exfoliative disorders and Steven Johnsons
Rarely alopecia, seizures, neutropenia, agranulocytosis, hypokalemia
Complications like bacteremia
Allergic manifestations and rarely anaphylaxis
Severe complications are more common in those with malignancies and AIDS and in those taking other medications. Most children requiring fluconazole therapy will have other underlying disorders.

Itraconazole

Trials summarized in tables

De wit 1998
Graybill 1998
Linpiyawan 2000
Mc Kinsey, 1999
Murray 1997
Phillips, 1998
Smith, 1991
De Repentigny,1996
Chariyalertsak, 2002
Mc Kinsey, 1999
Smith, 2001
Girois, SB
Crawford,F 2002
Mootsikapun P, 2003
Smith, DE 2001
Saag, MS 1999

1. Formulation proposed for inclusion

Oral formulations

Solution 10mg/ml

Capsule 100mg/cap

These two formulations are not bioequivalent. Solution has more applications and clinical evidence. Hence request is for solution only

Parenteral- 10mg/ml – not being requested

IV use can cause phlebitis and excipient related toxicity and is required only if patient is unable to tolerate oral formulation or has problems with gastric acidity

The oral and intravenous solutions are solubilised in hydroxy propyl β cyclodextrin.

2. International availability (sources)

Manufacturer- Janssen Pharma – Sporanox

Generic – Sandoz

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information including pharmacokinetics - Goodman and Gilman [20], Product information from Janssen Pharma, BNF for children.

This is also a synthetic triazole drug, absorbed well after oral administration. The capsule is better absorbed after food while the solution is better absorbed in the fasting state. Peak plasma concentrations obtained with solution can be 150% of that with capsule. In the plasma both itraconazole and its biologically active metabolite hydroxy -itraconazole are found in equal concentrations. More than 99% is bound to plasma proteins. Elimination half life is about 30 – 40 hrs. Steady state is reached only after many days and so loading dose is recommended. Pharmacokinetics is variable in children[41] especially those with cystic fibrosis, neutropenia, and AIDS. The drug is metabolised in the liver and so liver diseases increase drug levels. It is more hepato toxic than fluconazole. Hydroxypropyl β cyclodextrin

in the solutions is excreted primarily through the kidneys and can accumulate and cause toxicity if renal clearance is impaired.

Spectrum of activity is similar to that of fluconazole. Although there is cross resistance to different azole drugs in vitro, among Candida, clinically fluconazole resistant Candida infections may respond to itraconazole. Incidence of fluconazole resistant, AIDS related oropharyngeal candidiasis is about 5%. In addition, fluconazole resistance can develop in *C albicans* and other species, during treatment, due to a variety of mechanisms. Azole resistance can develop after prolonged therapy with itraconazole also. The drug has activity against dermatophytes and some agents of invasive fungal infections.

Therapeutic uses

Oropharyngeal and oesophageal candidiasis especially when patient is not responding to fluconazole and is not on drugs which interact with itraconazole is the main indication.
As an alternative drug in the treatment of non meningeal infections due to H capsulatum and B dermatitidis including infection in the HIV infected
Onychomycosis – is uncommon in children and terbinafine may be a better option
Sporotrichosis
As an alternative for the systemic therapy of tinea capitis, tinea corporis, tinea cruris and pityriais versicolar
It is not recommended for maintenance therapy of cryptococcal meningitis because of higher incidence of relapse

Dosage

For oral candidiasis, Itraconazole cyclodextrin oral solution (2.5 mg/kg body weight/dose administered twice daily for 7--14 days (maximum dose: 200mg/day- several adverse events are dose dependant). Solution is recommended for oral and oesophageal candidiasis and is to be taken fasting. It is to be swished in the mouth before swallowing. Oesophageal candidiasis will require treatment for 14 -21 days.
Itraconazole capsules and oral solution should not be used interchangeably because drug exposure is greater with the oral solution when the same dose of drug is administered.
For treatment of deep mycoses, loading - same dose three times a day for three days - can be used. For maintenance therapy of disseminated histoplasmosis in HIV infected, single daily doses are used.
Onychomycosis is treated with same dose once daily for 12 weeks or twice daily for one week each month. Drug is retained in the nail.
Patients should be monitored for adverse events, especially hepatic toxicity. Oral and oesophageal candidiasis can be diagnosed clinically and dermatophyte infections with the help of simple microscopy. Lab support is required for diagnosing invasive infections. Drug interactions should be considered while prescribing. Facility is required for monitoring.
Itraconazole is recommended for children in the following guidelines [4, 6, 12, 13]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

Oral and oesophageal candidiasis

A review has shown that clinical cure and mycological cure is similar to fluconazole in patients with oral candidiasis[26] as discussed under fluconazole. Studies in this review are summarised in table 1. Fluconazole-refractory OPC will respond to itraconazole solution in

approximately 50%--60% of patients [42]. It is as efficacious as fluconazole for oesophageal disease [43] and in children [41, 44, 45].

Dermatophyte infections

It is effective in the treatment of tinea capitis and other superficial fungal infections in children [46-49]. For onychomycoses, and ring worm infections of skin of foot itraconazole is better than no therapy[50, 51] . However in tinea umbricata the remission was short lived with itraconazole [52].

Histoplasmosis

A non randomised open label study showed that itraconazole is safe and effective as an alternative in treating mild to moderate histoplasmosis in the HIV infected[53] In children also itraconazole is useful for treating histoplasmosis [54].
In children, a dosage of 5mg/kg provides adequate serum levels[41, 45]

2. Summary of comparative evidence on safety

RCTs have shown that side effects are similar to that of fluconazole. A metanalyses of adverse events show that itraconazole has higher GIT related side effects, bronchospasm and cough and hepatic toxicity[40]. It can cause a dose dependant ionotropic effect and can lead to congestive cardiac failure. So it is contra indicated in individuals with ventricular dysfunction and in those at risk of developing heart failure. It should not be co-administered with drugs like Cisapride, quinidine, midozolam, dofetilide, levomethadyl, pinazide etc since serious CVS events including death can occur. There are several other drug interactions also. Allergy and skin manifestations including Steven Johnsons are also reported. Peripheral neuropathy, menstrual disorders and hypokalemia are also reported

There is insufficient data on adverse events from children. According to the drug information sheet from the company, the data available from a small number of children show that there are no major toxicities following administration of tablets or oral solution. Clinical studies on infants and children show this drug to be safe and effective in children with oropharyngeal candidiasis [41, 45]. In lab animals some bone changes were observed.
It is category C drug in pregnancy.

3. Summary of available data on comparative cost

10mg/ml solution for 150 ml US$ 122.39
100mg tab generic– for 15 – US$ 14.87 (Sandoz product list)

4. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Cost for one day at 100mg will be about US$ 8.2. This drug is more expensive than fluconazole. Adverse events are also more. So its use may be limited to only fluconazole refractory oro-pharyngeal and oesophageal candidiasis. Amphotericin B can be used in this situation, but itraconazole can be given orally and is less nephrotoxic. Drug cost is only one aspect of treating for fungal infections.
It is costlier than griseofulvin for treating dermatophyte infections.

5. Summary of regulatory status

FDA approved. Although BNF C states that capsules are not licensed for use in children below 12 yrs and that parenteral preparations are not licensed for use in children, indications for use and dosage for children 1 month old onwards is given in the same formulary

6. Availability of pharmacopoeial standards

Not available from USP and international pharmacopoeia

7. Proposed text for WHO model formulary

Itraconazole cyclodextrin- 10mg/ml oral solution.
This drug has activity against Candida species and dermatophytes

Use
Fluconazole refractory oropharyngeal and oesophageal candidiasis
Non meningeal infections due to *H capsulatum* and *B dermatitidis*
Onychomycosis and other dermatophyte infections requiring systemic therapy
Sporotrichosis
Dosage
2.5 mg/kg body weight/dose twice daily (maximum dose: 200mg/day)
For oral candidiasis treatment is for 7-14 days and for oesophagial infection 14 -21 days. The solution has to be swished in the mouth before swallowing.
For treatment of deep mycoses, loading - same dose three times a day for three days – is used.
For maintenance therapy of disseminated histoplasmosis in HIV infected, single daily doses are used.
Onychomycosis - same dose once daily for 12 weeks or twice daily for one week each month.
Absorption of solution is better if taken fasting
Contraindications
Ventricular dysfunction and risk factors for cardiac failure
Co-administration with drugs like Cisapride, quinidine, midozolam, dofetilide, levomethadyl, pinazide etc
Known hypersensitivity
Precautions
Several drugs interact with itraconazole. Several children requiring itraconazole therapy can have other underlying conditions. Consider these while prescribing
Patients should be monitored for adverse events, especially hepatic toxicity. Patients or caregivers should be informed of adverse events
Itraconazole capsules and oral solution should not be used interchangeably because bioavailability is different
Several adverse events are dose dependant.
Adverse reactions
Incidence of severe adverse events is low. Adverse events include hepatic toxicity
dose dependant ionotropic effect that can lead to congestive cardiac failure, several drug interactions, GIT related events like vomiting, abdominal pain, nausea, dyspepsia and diarrhoea, bronchospasm, head ache, skin manifestations like rashes and rarely exfoliative disorders and Steven Johnsons, allergic manifestations and rarely anaphylaxis.
In lab animals bone changes were observed.
Pregnancy - Category C

Ketoconazole tablets also can be used to treat oropharyngeal and oesophageal candidiasis at a dose of 5--10 mg/kg/day in 2 divided doses for 14 days, but it might be less effective than fluconazole or itraconazole solution because of more variable absorption. Also, Ketoconazole has been associated with endocrinologic abnormalities related to steroid metabolism, including adrenal insufficiency and gynecomastia.

Voriconazole is another triazole drug that can be used systemically. There is insufficient data for its superiority over other drugs for indications it may prove useful - invasive aspergillosis, fever in neutropenics, oesophageal candidiasis and salvage therapy of rare infections like those due to *P boydii* and fusarium. It is teratogenic (class D) and has other adverse effects similar to fluconazole. About 30% experience transient visual disturbances.

Ketoconazole and Voriconazole are not being requested for in the present application for reasons mentioned above

Amphotericin B

Trials summarized in tables

Arathoon 2002
Chavenet 1992
Dreissen,1996
Kontoyiannis D P,2001
Girois, SB 2005
Chotmongkol V,2005
Brouwer AE, 2004
Mootsikapun P, 2003

1. Formulation proposed for inclusion

Amphotericin B deoxycholate complex–50mg/vial lyophilised powder for IV use
This is on the complementary list of WHO essential drugs
Lipid formulations are available – Amphotericin B colloidal suspension, liposomal formulation, and amphotericn B lipid complex – these are not being requested for reasons discussed under costing and evidence for efficacy and toxicity
Oral formulation for intestinal candidiasis is available. This is not being requested for since other options with lesser toxicity are available for this indication.

2. International availability (sources)

MISSION, MEDS, JMS, IDA.

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug.

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information and pharmacokinetics– Goodman and Gillman[20] and BNF for children.

Amphotericin B is a polyene macrolide which acts primarily by binding to a sterol moiety present in the cell membrane of fungi, causing increase in permeability and leakage of small molecules. Gastro intestinal absorption of amphotericin B is negligible. After repeated IV infusions plasma levels fall to about 50% in 24 hrs. In the blood, the drug is released from its complex with deoxycholate but remains >90% bound to plasma proteins. Only 2 -5% of each dose is recovered from urine of patients on daily therapy. There is little penetration into CSF, vitrous humor or amniotic fluid. But, there is extensive binding to tissues especially liver and spleen. Therefore elimination half life is prolonged. There is variability in the pharmacokinetics of this drug in the neonates[55]

Amphotericin B has clinical activity against most fungi causing invasive infections like Candida spp, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Sporothrix schenkii*, Aspergillus spp, *Coccidioidis immitis*, *P marneffei* and agents of mucor mycoses. Some isolates of *C lusitaniae* and *Aspergillus terreus* may be resistant to this drug. However, significant amphotericin B resistance is very rare and out come of therapy

depends to a large extend on the hosts status. Lipid formulations are not clinically superior, but nephrotoxicity may be lower.

Indications for use

Amphotericin B is the drug of choice for several invasive fungal infections like mucormycoses, cryptococcal meningitis, candidemia and other forms of invasive candidiasis, severe histoplasmosis, blastomycosis, coccidiodomycosis, penicillioses etc. in children.

It is also used in severe candida oesophagitis especially those not responding to fluconazole and for disseminated cutaneous candidiasis in the new born.

It is one of the drugs used in patients with neutropenia who develop fever not responding to antibacterial therapy.

As once weekly therapy it may be used to prevent relapse in patients with AIDS successfully treated for cryptococcosis and histoplasmosis.

Dosage and duration

Can vary depending on the type of infection and response to therapy.
For invasive infections, 0.5-1.5 mg/kg is administered once daily. For meningeal and extrameningeal cryptococcosis, initial therapy is a combination of amphotericin B and flucytosine for a minimum of 2 weeks (induction). In cases where flucytosine can not be used, amphotericin B alone is given.
Treatment is continued until 2-3 weeks after the last positive culture and signs and symptoms have resolved.
For histoplasmosis, amphotericin B therapy is for 2--3 weeks (12 -16 wks in case of meningeal involvement) followed by 3--6 months of consolidation therapy.
For refractory oral and oesophageal candidiasis, low dose IV amphotericin B (0.3-0.5 mg/kg/day) for seven days can be used.

Administration

Amphotericin B is to be reconstituted following manufacturer's instructions. It is administered intravenously, in 5% dextrose in water to give a final concentration of 0.1 mg/ml, over 1--2 hours. For patients with azotemia, hyperkalemia, or who are receiving high dose (>1 mg/kg), a longer infusion time of 3--6 hours is recommended. Close observation is required while administering at least for 30 min. The drug is incompatible with sodium chloride.
Laboratory support is required for diagnoses of most infections requiring amphotericin B therapy and also for monitoring toxicity. This includes hepatic and renal function tests, blood counts and electrolytes estimation. Most children will have other underlying disorders.
Amphotericin B is recommended for children in the following guidelines [4, 6, 12-14]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

In a review analysing trials comparing Fluconazole and amphotericin B there was no significant difference in mortality, invasive fungal infections or colonisation in neutropenic

patients between treatments [39]. Authors suggest that there is likely to be bias in the study designs and amphotericin is to be preferred.

A meta analyses of trials using amphotericin B and Fluconazole for treating candidemia showed that amphotericin B and Fluconazole are equally effective in reducing overall and infection specific mortality and in bringing about microbiological cure in patients who are not severely immunocompromised and at low risk of death, irrespective of infecting species. However, there was a trend favouring amphotericin B for the treatment of non albians candida [28]. Details are summarised in table 3.

Trials on oropharyngeal candidiasis was included in a review and are summarised in table 1[26].

A multicentric RCT showed that amphotericin and fluconazole are equally effective in treating fever in neutropenic cancer patients not responding to antibacterial therapy[56]. A randomised trial has shown that Amphotericin with flucytosine is the best initial therapy for cryptococcal meningitis[57] in HIV infected adults.

There are not many trials in children using conventional amphotericin B. For neonatal septicaemia, conventional amphotericin B was found to be more toxic compared to fluconazole[58] A Cochrane review for treatment of invasive fungal infections in preterm infants found only one eligible study and this showed fluconazole to be at least effective as amphotericin B[32]. In children individualised dose adjustment is required within a range of 0.7 to 1mg/kg based on weight to get the most effective blood levels without toxicity. Lighter children may require 1.25 to 1.5mg/kg [59] Studies reporting on the pharmacokinetics of amphotericin in children saw inter patient variations in distribution and clearance[60, 61] Amphotericin B as lipid formulation was found effective and safe in 548 patients aged 0-20 [62]. There is no difference between formulations in clinical efficacy.

6. Summary of comparative evidence on safety

Adverse effect of amphotericin B is primarily nephrotoxicity[40] is dose dependant and exacerbated by use of concomitant nephrotoxic drugs. Nephrotoxicity can be reduced by hydration with I L 0.9% saline IV on the day of amphotericin B infusion. Infusion-related fevers, chills, nausea, and vomiting might occur, although they are less frequent in children than adults. Pre-treatment with acetaminophen or diphenhydramine can alleviate febrile reactions. Other rarer reactions include hypotension, arrhythmias, and allergic reactions, including anaphylaxis. Hepatic toxicity, thrombophlebitis, and anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures), also might occur.

Studies in children also report toxicity and show need for monitoring and dose adjustments[63].

Amphotericin B lipid formulations may have lesser nephrotoxicity. A metaanalyses shows that other types of toxicities may be similar or more [40].Three lipid formulations have been developed, including amphotericin B lipid complex (ABLC, Abelcet), liposomal amphotericin B (AmBisome), and amphotericin B cholesteryl sulfate complex (ABCD). Experience with these preparations among pediatric patients is limited. Some of them achieve lower blood levels than conventional amphotericin B and there is not enough

evidence for clinical superiority. The drugs are considerably more expensive than conventional amphotericin B.

7. Summary of available data on comparative cost

Median price is US$ 5.7942 per 50mg vial.

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Amphotericin B is a life saving drug, although its use is limited to a few serious infections which are not very common at a community level. Cost of a vial will be the approximate cost of drug per day. Other costs will include cost of hospitalisation, monitoring, management of adverse reactions etc.

Cost of lipid formulations for 50mg as daily dose can be from US$ 80 to 200 approximate.

9. Summary of regulatory status

FDA approved. Parenteral preparations – conventional and lipid formulations- are licensed for use in children.

10. Availability of pharmacopoeial standards

Listed in US pharmacopoeia, EU pharmacoepoeia and international pharmacoepoeia.

11. Proposed ext for WHO model formulary

Amphotericin B deoxycholate complex–50mg/vial lyophilised powder for IV use

This antifungal drug has a broad spectrum of activity

Uses in children

Drug of choice for invasive and serious fungal infections - mucormycoses, cryptococcal meningitis, candidemia and other forms of invasive candidiasis, severe histoplasmosis, blastomycosis, coccidiodomycosis, penicillioses

Severe candida oesophagitis especially those not responding to fluconazole

Disseminated cutaneous candidiasis in the new born

Fungal infections not responding to fluconazole

Fever in patients with neutropenia not responding to antibacterial therapy

As once weekly therapy to prevent relapse in patients with AIDS successfully treated for cryptococcosis and histoplasmosis.

Dosage

Initial therapy for invasive fungal infections - 0.7--1.5 mg/kg body weight/day for a minimum of 2 weeks

For cryptococcal infections, flucytosine is administered together with amphotericin B.

For candidemia, continue treatment for 2-3 weeks after signs and symptoms have resolved and the last positive blood culture

For histoplasmosis, treat for 2--3 weeks (12 -16 wks in case of meningeal involvement) followed by 3--6 months of consolidation therapy

For refractory oral and oesophageal candidiasis, 0.3-0.5 mg/kg/day for seven days

Administration

Amphotericin B is to be reconstituted following manufacturer's instruction. It is administered in 5% dextrose in water to give a final concentration of 0.1 mg/ml, intravenously over 1--2 hours, immediately following reconstitution. For patients with

azotemia, hyperkalemia, and for those receiving high dose (>1 mg/kg), a longer infusion time of 3--6 hours is recommended. Observe closely at least for first 30 min. Sodium chloride should not be used for diluting.

Contraindications

Renal failure

Precautions

Nephrotoxicity can be reduced by hydration with I L 0.9% saline IV on the day of amphotericin B infusion.

Pretreatment with acetaminophen or diphenhydramine can alleviate febrile reactions. Laboratory support is required for diagnoses of most infections requiring amphotericin B therapy and also for monitoring toxicity. This includes hepatic and renal function tests, blood counts and electrolytes estimation. Patients can have other underlying illnesses and are hospitalised

Adverse reactions

Adverse effect of amphotericin B is primarily nephrotoxicity. This is dose dependant and exacerbated by concomitant use of nephrotoxic drugs

Infusion-related fevers, chills, nausea, and vomiting might occur, although they are less frequent in children than adults.

Other rarer reactions include hypotension, arrhythmias, and allergic reactions, including anaphylaxis. Hepatic toxicity, thrombophlebitis, and anemia, and rarely neurotoxicity (manifested as confusion or delirium, hearing loss, blurred vision, or seizures), also might occur.

Flucytosine

Trials summarized in tables

Brouwer AE, 2004
Saag, MS 1999

1. Formulation proposed for inclusion

Flucytosine 250 mg capsule (or 500mg capsule) - is listed on the WHO complementary list of essential drugs
Parenteral preparation 10mg/ml – not being requested for flucytosine is well absorbed from GIT

2. International availability (sources)

Manufacturer- Ancobon -Valeant pharmaceuticals, USA

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information and pharmacokinetics – Goodman and Gilman [20], Drug information from Valeant Pharma anad BNF for children

Flucytosine is a fluorinated pyrimidine which is deaminated inside the fungus to 5 – fluorouracil, by susceptible fungi. This inhibits DNA synthesis. The enzyme required for the deamination is present only in very low levels in mammalian cells. It is absorbed well from the GIT and is widely distributed in the body including CSF. Peak levels are achieved in 1-2 hrs after a dose and half life is about 3-6hrs. Although the kinetics is similar in children, individual variability is higher. Half life is more in infants (median 7.4hrs). About 80% is excreted unchanged in urine. When renal clearance is decreased, drug can accumulate. Kinetics is variable in neonates[55]

The drug has action on *Cryptococcus neoformans*, candida species and agents of chromoblastomycosis. Monotherapy with this drug can lead to emergence of resistance and clinical failure or relapse and so is not recommended.

Indications for use

It is used along with amphotericin B for the initial treatment of Cryptococcal (pulmonary and meningeal) infections. The dose recommended for children is 25 mg/kg/dose (upto50mg/kg) orally four times daily for a minimum of 2 weeks.
Combination of fluconazole and flucytosine is superior to fluconazole alone for induction [17] and is an alternative to amphotericin B combination. This combination has more toxicity than fluconazole alone. There is little data in children on this combination.

Flucytosine has been used in combination with amphotericin B for severe invasive candidiasis, especially endocarditis[6] and with CNS disease
Dose has to be adjusted in renal impairment. Since it is administered along ith amphotericin B, a nephrotoxic drug, close monitoring is required.
Advanced laboratory support is needed for its use.
Flucytosine is recommended for children in the following guidelines [4, 6, 12, 13] and several reviews on antifungals in children.

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

A randomised trial has shown that clearance of cryptococci from CSF was significantly faster when amphotericin B and flucytosine were used together as compared to amphotericin alone, amphotericin and fluconazole together and triple therapy[57]. Anecdotal reports show it is safe and effective in children for this indication[64, 65].
Comaparison has showed that flucytosine administered either orally or IV is equally effective[66]**.**

6. Summary of comparative evidence on safety
There is not much data from children. The product information from the company says that in a small number of neonates treated for candidiasis there were no unexpected adverse reactions. Drug levels can exceed acceptable levels in the young [67] and so needs monitoring and dose adjustment.
Flucytosine has the potential for considerable toxicity. It can cause bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia. Skin rashes, nausea, vomiting, diarrhoea and severe enterocolitis can occur. Reversible hepatic toxicity is reported. Toxicity is more in those with AIDS, renal impairment and in those with other risk factors for bone marrow suppression. Hypokalemia, acidemia, CVS and CNS adverse events are reported. It is category C for pregnancy.
Monitoring of drug levels (between 40--60 μg/ml) and dose adjustments are recommended. However, evidence shows that oral use for limited periods are safe [66]. The drug should be avoided among children with severe renal impairment.

7. Summary of available data on comparative cost
500 mg tab US$ 11 per tab.

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)
The drug is expensive, but there is no alternative for induction therapy in cryptococcal disease. Monotherpay with amphotericin B or fluconazole, as the evidence stands, is inferior. Cost of drugs is only one aspect of he expenses.

9. Summary of regulatory status
FDA approved. Tablets are not licensed in the UK but can be obtained on named patient basis.

10. Availability of pharmacopoeial standards
Listed in US, EU and international pharmacoepoeia.

11. Proposed text for WHO model formulary

Flucytosine 250 mg capsule
The drug has action on Cryptococcus neformans and Candida species. However, it is not recommended for monotherapy.

Uses
For the initial treatment of Cryptococcal (pulmonary and meningeal) infections, along with amphotericin B preferably or with fluconazole
Severe invasive candidiasis including endocarditis, along with amphotericin B or fluconazole
Dosage
25 mg/kg/dose orally four times daily for of 2 weeks
Dose has to be adjusted in renal impairment.
Contraindications
To be used with caution in patients with renal impairment, liver and blood disorders
Precautions
Monotherapy should be avoided
Since it is usually administered along with amphotericin B, a nephrotoxic drug, close monitoring is required. Monitor for renal and hepatic function and blood counts.
Monitoring of drug levels (between 40--60 μg/mL) and dose adjustments based on levels are recommended. However, oral use for limited periods may be safe
Advanced laboratory support is needed for its use and children requiring this drug can have other serious illnesses
Adverse events
Flucytosine has the potential for considerable toxicity. It can cause bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia. Skin rashes, nausea, vomiting, diarrhoea and severe enterocolitis can occur. Reversible hepatic toxicity is reported. Hypokalemia, acidemia, CVS and CNS adverse events are reported. Toxicity is more in those with AIDS, renal impairment and in those with other risk factors for bone marrow suppression. It is category C for pregnancy.

Caspofungin

Trials summarized in tables

Arathoon 2002
Villanueva A, 2002

1. Formulation proposed for inclusion
Caspofungin acetate 50mg per vial and 70 mg per vial for IV injection
Request is for inclusion in complementary list

2. International availability (sources)
Merck – trade name Cancidas

3. Whether listing is requested as individual drug or as an example of a therapeutic group
As individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)
Reference for general information and pharmacokinetics – Goodman and Gilman [20], Drug information from Merck and BNF for children

Caspofungin is an echinocandidin which acts by inhibiting fungal cell wall synthesis. This semi synthetic lipo peptide is water soluble. It is not absorbed from GIT. After IV injection half life is about 9-11hrs. The drug is metabolised and metabolites excreted in urine and faeces. The drug is widely distributed in tissues. Hepatic insufficiency increases drug levels in blood. Renal impairment has no effect. It has activity against candida including azole resistant candida [68]. There is activity against Aspergillus species as well[69]. There is no activity against *Cryptococcus neoformans* or *Histoplasma capsulatum.* Concomitant use of cyclosprin can increase caspofungin blood levels and rifampin can reduce it[70].

Indications for use
Invasive aspergillosis when patients are intolerant to first line drugs (amphotericin B) and /or are not responding to therapy [71]. – FDA approved
Oesophagial candidiasis – FDA approved
Deep and invasive candidiasis. (FDA approved). In treating candidiasis, this drug is likely to be effective in cases of fluconazole failures.
Empirical therapy for fever in neutropenic patients – FDA approved

Dosage
The drug is administered as IV once daily over 1 hour. Experience is limited in children, and a definitive pediatric dose has not been defined. Preliminary pharmacokinetic data on caspofungin among children indicate that a daily intravenous dose of 1.5 mg/kg or 50 mg/m^2/day [72] is required to provide exposure similar to that seen in adults receiving 50 mg/day. (The adult dosage is 70mg on day one and 50 mg per day thereafter.)

Dosage adjustment may be required in hepatic insufficiency and also when co-administered with drugs with interactions, like rifampin
Advanced laboratory support is required for diagnosing invasive infections requiring therapy. Therapy for oesophageal candidiasis can be based on clinical grounds.
Caspofungin is recommended for children in the following guidelines [4, 6] and in reviews[73]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

Caspofungin is effective and comparable to amphotericin B and fluconazole for treatment of oesophageal *Candida* infections and comparable to amphotericin B for treatment of candidemia in adults [74, 75]. A multi centric randomised double blind study comparing caspofungin and amphotericin B, showed that caspofungin cured more patients (difference not statistically significant) with oral and oesphagial candidiasis with HIV infection and had fewer side effects[76]. It was useful in treating cases of fluconazole failure [77]. Other studies also show that caspofungin is useful in treating oesophageal and invasive candidiasis[78] and the effect is as good as fluconazole or amphotericin B [79, 80]
A review of four clinical trials showed that caspofungin is effective in treating invasive candidiasis and invasive aspregillosis in patients with neutropenia[81].
Data from manufacturer on phase 111 studies show efficacy of caspofungin comparable to amphotericin B for indications approved by FDA.
It has synergistic action with other antifungals and so may prove useful in treating difficult to treat life threatening infections [82].
Although the evidence on the efficacy and safety of this drug in adults is increasing, data from children is probably insufficient to make firm recommendations. Studies on small numbers of children show that the drug is safe [72]. A report on 20 children receiving this drug for proven or probable invasive fungal infection shows that this drug is effective and safe in children [83]. It is also found useful in combination therapies in children[84]

6. Summary of comparative evidence on safety

This drug is well tolerated by adults and also children [72], from evidence so far. Phlebitis at the site of injection is possible.
In a retrospective evaluation of 25 immunocompromised children who received caspofungin, the drug was well tolerated, and only three patients had adverse events that might have been related to the drug (hypokalemia in all three children, elevated bilirubin in two, and decreased hemoglobin and elevated alanine aminotransferase in one)[4, 85]. Maintenance dose adjustment may be required in hepatic insufficiency [82]. Adverse events are significantly less compared to amphotericin B [74]. Available data indicate that caspofungin is safe in children[6].
Based on drug level data, when rifampicin is used along with caspofungin, maintenance dose of caspofungin may need to be increased[70]
It is pregnancy category C drug. Long term adverse events if any, are not fully known.

7. Summary of available data on comparative cost

Manufactured by Merck
50 mg vial costs US$ 440 and 70 mg vial US$ 567

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Compared to conventional amphotericin B, this rug is very expensive. It is for use in patients where amphotericin B is ineffective or when it cannot be tolerated. Another potential use is as combination therapy for life threatening infections [82, 84]. Cost of drugs is only a part of total cost for antifungal therapy

9. Summary of regulatory status

FDA approved. BNF C states that it is not licensed for use in children but gives indications for therapy in children and dosage

10. Availability of pharmacopoeial standards

Not available from US, EU and international pharmacopoeia

11. Proposed text for WHO model formulary

Caspofungin acetate 50mg per vial and 70 mg per vial for IV injection. This drug has action on Candida species and Aspergillus species.

Uses

Oesophagial candidiasis refractory to treatment with conventional therapy

Deep and invasive candidiasis refractory to conventional therapy

Invasive aspergillosis when patients are intolerant to first line drugs or are not responding to therapy

Empirical therapy for fever in neutropenic patients not responding to antibacterial therapy

Dosage

A definitive pediatric dose has not been defined. Preliminary pharmacokinetic data indicate that a daily dose of 1.5 mg/kg or 50 mg/m^2/day is adequate and safe. The drug is administered as IV once daily over 1 hour.

Dosage adjustment may be required in hepatic insufficiency and also when co-administered with drugs that interact

Precautions

Use with caution in children with liver diseases.

Consider drug interactions while prescribing

Adverse events

Available data shows that this drug is well tolerated by children. Phlebitis at the site of injection is possible. Other reported events are nausea, vomiting, dyspnoea, tachycardia, flushing, fever, hypokalemia, elevated bilirubin levels, decreased hemoglobin levels and elevated alanine amino-transferase levels.

It is pregnancy category C drug.

Griseofulvin

Trials summarized in tables

Crawford,F 2002

1. Formulation proposed for inclusion

Griseofulvin for oral use - 125mg/tab-cap or 250mg/ tab-cap (microsize)
Both are on WHO essential drug list
Oral suspension also available – not being requested since dosages for administration are more accurate with tab-cap. Suspension is not licensed for use in the UK
Ultramicrosize particles are better absorbed but much more expensive

2. International availability (sources)

125mg tab-cap – IDA, DURBIN, IMRES, MISSION, ACTION, ORBI
250 mg tab - MEDS

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug.

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information - Goodman and Gilman [20], BNF for children

Griseofulvin is fungistatic and action is by inhibiting fungal mitosis. Absorption and blood levels after oral administration are variable. The absorption of ultramicrosized powders is better compared to microsize formulation. Half life is about one day. Griseofulvin gets deposited in keratin precursor cells, providing resistance to fungus invasion. Therefore, effect of treatment is first seen on new growth of hair and nails. Infection free tissue replaces the fungus containing tissue after it is shed. All types of dermatophyte infections of skin, nails and hair, respond to this drug. However it should not be used if topical applications are likely to be effective. This is because it has carcinogenic and teratogenic effects in laboratory animals. Although dermatophytes are susceptible to griseofulvin, treatment failures are not rare.

Indications for use

Ring worm infections like tinea capitis (infections involving hair), tinea cruris and corporis (infections of skin), tinea of hands and beard respond well to griseofulvin
For infections involving only skin topical therapy is to be preferred where possible.
It can be used for onichomycosis (nail infection). However, Itraconazole or terbinafine is preferred for toe nail infections.
Recommended dosage is 5-15mg/kg in childen in two or four divided doses. Treatment is continued till infected tissue is replaced by normal tissue, which is about a month for skin and hair infections and several months for nail infections. It is not useful for treating subcutaneous infections.

This drug is mentioned in a WHO guideline for children [19].

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

A review of 12 trials for the treatment of fungal skin infections of the foot showed that griseofulvin can bring about cure but terbinafine is more effective[51]. Another review on treatment of onichomycoses found that here was no difference between itraconazole, ketoconazole and griseofulvin in cure rates, but, terbinafine is better [50]. A meta-analyses of 6 randomised clinical trials for childhood tinea capitis comparing griseofulvin with terbinafine showed that griseofulvin for 6- 8wks is similar to terbinafine for 2-4wks [86] for treating Trichophyton infections. Five studies identified trichophyton as the predominant species causing infection. However, griseofulvin may be better for infections due to microsporum species. Another RCT in children show that cure rates for tinea capitis is low with griseofulvin[38] A randomised trial for treatment of tinea imbricata showed that griseofulvin and terbinafine are effective[52].

6. Summary of comparative evidence on safety

Incidence of serious adverse events is very low. The meta analyses comparing griseofulvin and terbinafine did not find any significant side effects in children [86]. Head ache, which disappears when therapy is discontinued, can occur in 15%. Other recorded side effects include peripheral neuritis, lethargy, dizziness, confusion, syncope, vertigo, blurred vision, transient macular oedema, and augmentation of the effects of alcohol. These can affect skilled work. GI side effects like nausea, vomiting, diarrhoea can occur. Hepatotoxicity also has been observed. Hematologic effects include leukopenia, neutropenia, punctate basophilia, and monocytosis; these often disappear despite continued therapy. Blood studies should be carried out at least once a week during the first month of treatment or longer. It can cause renal effects like albuminuria without renal insufficiency. Reactions involving the skin are urticaria, photosensitivity, lichen planus, erythema, erythema multiforme–like rashes, and vesicular and morbilliform eruptions. Serum sickness syndromes and severe angioedema develop rarely during treatment with griseofulvin. It can cause exacerbation of SLE. Estrogenlike effects have been observed in children.

It increases the rate of metabolism of warfarin and so adjustment of the dosage of the latter may be necessary. The drug may reduce the efficacy of low-estrogen oral contraceptive agents.

7. Summary of available data on comparative cost

125 mg – US$ 0.0118/tab-cap
250 mg – US$ 0.0354/tab-cap

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Griseofulvin is useful and inexpensive alternative for systemic therapy of dermatophyte infections. Cost of drug per day is about US $ 0. 06 to 0.1 This drug has very few side effects.

9. Summary of regulatory status

FDA approved. Suspension not licensed for use in the UK.

10. Availability of pharmacopoeial standards

Listed in US pharmacopoeia, international pharmacopoeia, EU pharmacopoeia.

11. Proposed text for WHO model formulary

Griseofulvin for oral use - 125mg/tab-cap. This drug has activity on dermatophytes.

Uses

Ring worm infections - tinea capitis, tinea cruris, tinea corporis and onichomycosis

Dosage

5-15mg/kg in two or four divided doses

Treatment is continued till infected tissue is replaced by normal tissue, which is about a month for skin and hair infections and several months for nail infections.

Contraindications

Systemic lupus erythematosus, porphyria

Liver diseases

Precautions

For infections involving only skin topical therapy may be preferred.

Itraconazole or terbinafine is preferred for toe nail infections. It is not useful for treating subcutaneous infections.

Monitor blood count once a week during the first month of treatment or longer. Inform patient or care giver about possible adverse events

It increases the rate of metabolism of warfarin and so adjustment of the dosage of the latter may be necessary. The drug may reduce the efficacy of low-oestrogen oral contraceptive agents.

Avoid in pregnancy

Adverse events

Incidence of serious adverse events is very low. Its use can affect performance of skilled work. Head ache, which disappears when therapy is discontinued, can occur. Other recorded side effects include peripheral neuritis, lethargy, confusion, syncope, vertigo, blurred vision, transient macular edema, and augmentation of the effects of alcohol. GI side effects like nausea, vomiting, diarrhea can occur. Hepatotoxicity also has been observed. Hematologic effects include leukopenia, neutropenia, punctate basophilia, and monocytosis; these often disappear despite continued therapy. It can cause renal effects like albuminuria without renal insufficiency. Reactions involving the skin are urticaria, photosensitivity, lichen planus, erythema, erythema multiforme–like rashes, and vesicular and morbilliform eruptions. Estrogenlike effects have been observed in children.

Terbinafine

Trials summarized in tables

Crawford,F 2002[7]
Rich, P 2001[13]
Smith S, 2001[14]

1. Formulation proposed for inclusion

Terbinafine 250 mg tablet
Terbinafine 1% cream

2. International availability (sources)

Terbinafine generic - several manufacturers – Teva, Gideon Richter USA, Mylan pharma, Invagen pharms, Reddys labs, Ranbaxy, Genpharm, Watson lab
1% cream –Taropharms North
Lamisil (tab and cream) distributed by Novartis, USA

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug.

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

References for general information - Goodman and Gilman[20], Drug information from Novartis, BNF C
Terbinafine hydrochloride is a synthetic allylamine compound. It is absorbed from the GIT but has low bioavailability. The drug accumulates in the skin, nail and fat. The half life can extend to 200 to 400 hrs. It has in vitro activity against dermatophytes and *Candida albicans*. The drug is well tolerated when taken orally. There are drug interactions. Levels of drugs like tricyclic antidepressants, beta blockers, monoamine oxidase inhibitors type B, and serotonin reuptake inhibitors can be elevated. It decreases clearance of caffeine and increases clearance of cyclosporine.
A small percentage of topically applied drug can be absorbed, but plasma levels are many times lower than that achieved after oral administration

Use and dosage

The tablet can be used for treating onychomycosis and other dermatophyte infections requiring systemic therapy. Recommended dosage schedule for children and has varied. For children over 1 year, 10-20 kg – 62.5 mg once daily; 20-40kg -125mg once daily; > 40 kg 250mg once daily. Adult dose is one 250mg tablet daily.
As 1% cream, applied twice daily for one to two weeks is effective for tinea corporis, tinea cruris and tinea pedis. It can be used for candidiasis and tinea versicolor, but may be less effective.
It should not be used for oral, vaginal or ophthalmic application.
This drug is recommended in a WHO guideline [13]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection,/exclusion of particular data)

Tinea capitis

A meta-analyses of 6 randomised clinical trials for childhood tinea capitis comparing griseofulvin with terbinafine showed that terbinafine for 2-4wks is similar to griseofulvin for 6- 8wks [86] for treating Trichophyton infections. Five studies identified trichophyton as the predominant species causing infection. Recent data from children show that terbinafine is effective for *Microsporum species* infections also[87-89]

Onychomycoses

A review on clinical trials for treatment of onichomycoses found that terbinafine is better than griseofulvin, itraconazole and ketoocanazole for this indication [50]. It is safe and effective in children also for this indication[90, 91]. Recent evidence show continuous treatment is better[92].

Other superficial infection

A review of 12 trials for the treatment of fungal skin infections of the foot also showed that oral terbinafine is better than griseofulvin [51]. A randomised trial for treatment of tinea imbricata showed that griseofulvin and oral terbinafine are equally effective[52] Successful use of oral therapy in tinea imbricata is reported from other parts of the world also[93].
Randomised open label studies have shown that single oral daily dose terbinafine is useful in treating tinea corporis or tinea cruris [94] and tinea pedis [95] in patients with HIV infection
Topical applications have been found useful , including in children, for treating tinea cruris, tinea corporis and tinea pedis[96, 97]

6. Summary of comparative evidence on safety

Terbinafine is well tolerated orally. The meta analyses on childhood tinea capitis did not show any significant adverse events and the events were similar in griseofulvin and terbinafine treatment groups[86]. The adverse events on oral therapy include GI effects, head ache, rash and rarely Steven Johnson syndrome. Rare hepato toxicity is reported with oral therapy and is not recommended in patients with renal or hepatic failure. Exacerbations of SLE can occur and retina and lens changes are also recorded following oral therapy. Reversible agranulocutosis is reported in a child. [98]. It is Category B for safety in pregnancy. Long term adverse effects, like carcinogenicity, require more data.

Topical application has minimal adverse effects and is related to application site reactions.

7. Summary of available data on comparative cost

250mg tab – US$ 81.6 for 28
1% cream 30gm – US$ 17.99.

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

It is more expensive than griseofulvin. Overall costs will be US$ 81 for 4wks of oral treatment of terbinafine compared to US$ 10 (approximate) for griseofulvin. There seems to be clinical superiority for this drug and better chances of compliance.

9. Summary of regulatory status

FDA approved. BNF C states that it is not licensed for use in children but lists dosage and indications.

10. Availability of pharmacopoeial standards

Not available from US, EU and international pharmacopoeia.

11. Proposed text for WHO model formulary

Terbinafine 250 mg tablet
Terbinafine 1% cream

Uses
Tablet – onychomycosis and other ring worm infections requiring systemic therapy
1% cream - tinea corporis, tinea cruris and tinea pedis, candidiasis involving skin only and tinea versicolor
Dosage
Dosage schedule for children is not yet final. For children over 1 year and weighing 10-20 kg – 62.5 mg once daily;
20-40kg -125mg once daily;
> 40 kg - 250mg once daily.
Adult dose is one 250mg tablet daily.
1% cream is applied twice daily
Contraindications
Renal or hepatic failure
Precautions
It should not be used for oral, vaginal or ophthalmic application.
Adverse events
Terbinafine is well tolerated orally. Following oral therapy, there can be GI effects, head ache, rash and rarely Steven Johnson syndrome. Rare hepato toxicity is reported. Exacerbations of SLE and retina and lens changes are also recorded.
It is Category B for pregnancy.
Topical application has minimal adverse effects and is related to application site reactions.

Clotrimazole

Trials summarized in tables

Linpiyawan 2000
Murray 1997
Pons, 1993
Redding, 1992
Powderely,1995

1. Formulation proposed for inclusion

10mg troches for dissolving in the mouth
1% cream for topical use on skin
100mg pessary for vaginal use – already in WHO essential drug list
(Solutions, powders, sprays etc are also available)

2. International availability (sources)

1% cream – MEDS, UNFPA, MISSION, JMS, IMRES, IDA, ORBI, ACTION, DURBI
100 mg pessary – MISSION, UNFPA, IMRES, JMS, ORBI
10mg Troche/lozenge – Generic - Roxane, Paddock
Mycelex- Bayer pharms

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information - Goodman and Gilman [20], Drug information from Bayer and BNF for children

Clotrimazole is an azole drug only for topical use. After application on skin, 0.5% is absorbed. About 3 to 10% is absorbed after vaginal application. It is effective against candidiasis and dermatophyte infections.

Indications for use

Cutaneous candidiasis – twice a day applications are recommended. Cure rate is 80 to 100%
Vaginal candidiasis – vaginal cream or vaginal tablets at bed time cures about 80% of cases. Duration may be 7 days, 3 days or single use depending on the strength of the tablet (100mg, 200 mg or 500mg respectively)
Oral and pharyngeal candidiasis – 10 mg troches are to be dissolved slowly in the mouth four to five times a day for 14 days. Cure rate is near 100%.
Cure rate for dermatophyte infections of the skin is between 60 to 100%. Topical applications are not effective if hair or nails are involved.
Resistance to clotrimazole can develop as a consequence of previous exposure to clotrimazole itself or to other azole drugs leading to treatment failure.
For dermatophyte infections, ideally, skin scrapings should be examined before initiating therapy. Topical preparations containing combination of clotrimazole and corticosteroid are available and often misused. This combination is not shown to have additional benefits as

compared to clotrimazole alone and has side effects related to corticosteroid. It is more expensive as well[99].
Clotrimazole is recommended for children in the following guidelines [4, 6, 12, 13]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

A review analysing clinical trials on treatment oropharyngeal candidiasis in the HIV infected found that no difference in clinical cure between Fluconazole and clotrimazole (2 RCTs; n=358; RR 1.14; 95% CI 0.92 to 1.42). When compared with clotrimazole, both fluconazole (2 RCTs; n=358; RR 1.47; 95% CI 1..16 to 1.87) and itraconazole (1 RCT; n=123; RR 2.20; 95% CI 1.43 to3.39) showed better for mycological cure[26].
A randomised trial showed that topical Clotrimazole for 4 wks has similar effect as terbinafine for 1 wk in treating tinea pedis [97].1% clotrimazole is effective in treating dermatophyte infections[100].
Clotrimazole vaginal cream and tablets are effective in treating vaginal candidiasis and results comparable to oral fluconazole[99]

6. Summary of comparative evidence on safety

Topical clotrimazole is well tolerated. About 5% of patients using troches can develop GI irritation. Skin use can cause stinging, vesicles, desquamation, pruritus and urticaria. Vaginal use can result in burning sensation, urinary frequency and lower abdominal pain.
Although this drug is used in children, there is not sufficient documented data from this group.
It is pregnancy category C drug

7. Summary of available data on comparative cost

1% cream – US$ 0.024/gm
100mg pessary – US$ 0.0605/pessary
10 mg troche/lozenge – US$ 99.99 for 70

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

This is a topical application for common superficial fungal infections. Miconazole cream US$ 0.0163/gm

9. Summary of regulatory status

All formulations FDA approved and BNF C states that it is licensed for use in children.

10. Availability of pharmacopoeial standards

Listed in US pharmacopoeia and EU pharmacoepoeia.

11. Proposed text for WHO model formulary

Clotrimazole - 10mg troches for dissolving in the mouth
1% cream for topical use on skin
100mg pessary for vaginal use

Uses and dosage

Cutaneous candidiasis – twice a day applications

Vaginal candidiasis – vaginal cream or vaginal tablets at bed time for 7days

Oral and pharyngeal candidiasis – 10 mg troches are to be dissolved slowly in the mouth four to five times a day for 14 days

Dermatophyte infections of the skin – twice daily apllications

Precautions

Topical applications are not effective if hair or nails are involved.

Resistance to clotrimazole can develop following exposure to clotrimazole or other azole drugs leading to treatment failure.

Topical preparations containing combination of clotrimazole and corticosteroid are not recommended.

Adverse events

Clotrimazole is well tolerated. Patients using troches can develop GI irritation.

Skin use can cause stinging, vesicles, desquamation, pruritus and urticaria.

Vaginal use can cause burning, urinary frequency and lower abdominal pain.

There is not sufficient data in children especially below three years.

It is pregnancy category C

Miconazole

Trials summarized in tables

Van Roey, 2004

1. Formulation proposed for inclusion

2% Miconazole nitrate cream – already in WHO essential drug list
100mg vaginal pessary
(powder, spray etc are available)

2. International availability (sources)

2% cream – UNFPA, IMRES, MISSION, IDA, DURBIN, ORBI
100mg pessary – generic available – Actavis Mid atlantic, Perrigo

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information – Goodman and Gilman [20] and BNF for children
Miconazole penetrates stratum corneum and persists there for more than 4 days after application. It can be used as an alternative to clotrimazole for treating tinea pedis, tinea cruris and tinea versicolor and also for vulvo vaginal candidiasis. Cure rates are quite high with this drug also.
It is recommended for use in WHO guidelines[13, 14]

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

Miconazole has been found at least equal to nystatin in treating vaginal candidiasis [101] 2% miconazole cream is as effective as more recent topical antifungals for treating infections due to dermatophytes [102]. For diaper dermatitis 0.25% miconazole nitrate is safe and effective[103]

6. Summary of comparative evidence on safety

Side effects are very few[102, 103] and include burning, itching, irritation, head ache, and rash. Abdominal pain can occur after vaginal application. In children also there are no significant toxicities[104]

7. Summary of available data on comparative cost

2% cream – US$ 0.0163/gm

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Cost of clotrimazole 1% cream is – US$ 0.024/gm

9. Summary of regulatory status

FDA approved. Licensed for use in children Over the counter medication.

10. Availability of pharmacopoeial standards

Listed in US pharmacopoeia and EU pharmacoepoeia.

11. Proposed text for WHO model formulary

Miconazole nitrate - 2% cream
100mg vaginal pessary

Uses

Treatment of neonatal fungal skin infections, tinea pedis, tinea cruris and pityiasis versicolor and vaginal candidiasis

Dosage

Apply one to two times a day

Precautions

Topical applications are not effective if hair or nails are involved.

Resistance can develop following exposure to azole drugs leading to treatment failure.

Adverse events

Adverse events are very few and include burning, itching, irritation, head ache, and rash. Abdominal pain can occur after vaginal application

Nystatin

Trials summarized in tables

MC Phail 1996
Nyst, 1992
Pons,1997

1. Formulation proposed for inclusion

Tab-cap 100,000 units per cap – included in WHO essential drug list
Oral suspension – 100,000 units per ml
Pessary for vaginal use – 100,000 units – included in WHO essential drug list
(Also available as powder, cream and ointment)
Oral suspension is probably better than tab-cap for the drug to come into contact with lesions in mouth and pharynx and since there is little absorption from GIT

2. International availability (sources)

Tab –cap – MISSION, UNFPA, IDA, JMS
Oral suspension – MISSION, IDA, IMRES, DURBIN, JMS, UNFPA
Pessary - MISSION, IDA, IMRES, DURBIN, JMS, UNFPA, ACTION, ORBI

3. Whether listing is requested as individual drug or as an example of a therapeutic group

As individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information– Goodman and Gilman[20] and BNF for children
Nystatin is a polyene antifungal related to amphotericin B and used for topical applications only. It is not absorbed form GIT, skin or vagina.
It is effective only for the treatment of oral, pharyngeal, cutaneous and vaginal candidiasis. Powder is preferred for moist lesions.
Dose for infants for oral candidiasis is 2ml and for children and adults, 4-6 ml. This has to be swished in the mouth and swallowed four times a day for 7 days
For skin infections, the drug has to be applied two to four times a day.
Therapy can be initiated on clinical grounds
Nystatin is recommended for children in the following guidelines [4, 6, 12-14]
For vaginal infections, one pessary is inserted at night for 14 days

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection, /exclusion of particular data)

As discussed above nystatin can bring about clinical cure in patients with oral and pharyngeal candidasis but may be inferior to other drugs[26]. Nystatin is as probably as effective as miconazole in treating vaginal candida infections[101].

6. Summary of comparative evidence on safety

There are no side effect other than bitter taste and nausea. Bitter taste can interfere with compliance. In children also it is safe[27, 105]. Allergic reactions are very uncommon

7. Summary of available data on comparative cost

Tab- cap – US$ 0.0197/tab
Oral suspension – US$ - 0.0260/ml
Pessary –US$ - 0.0181/pessary

Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

It is cheaper than clotrimazole pessary.
Oral suspension for treatment of oral candidiasis is cheaper than formulations of fluconazole and clotrimazole for the same purpose
Cost of creams is similar to that of miconazole and clotrimazole creams

8. Summary of regulatory status

FDA approved

9. Availability of pharmacopoeial standards

Listed in US, EU and international pharmacoepoeia

Proposed text for WHO model formulary

Nystatin - Tab-cap 100,000 units per cap
Oral suspension – 100,000 units per ml
Pessary for vaginal use – 100,000 units
Cream – 100,000 units /4gm

This drug has action on Candida species and is for topical use.

Uses
Oral, pharyngeal, cutaneous and vaginal candidiasis
Dosage
Oral candidiasis - infants - 2ml; children - 4-6 ml
This has to be swished in the mouth and swallowed four times a day.
Vaginal – one pessary at night for 14 days
Cutaneous – Apply 2-4 times a day for 7 days
Precautions
Powder is preferred for moist skin lesions.
Adverse events
No adverse events other than bitter taste and nausea. Bitter taste can interfere with compliance. Allergic reactions are very uncommon

Whitfield's ointment

1. Formulation proposed for inclusion

This is an ointment containing 6% benzoic acid and 3% salicylic acid.

2. International availability (sources)

The ointment is available as a commercial preparation as tubes of 20 gms and bottles of 100gms and also can be made locally from the components.

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

Reference for general information – Goodman and Gilman and BNF for children

Benzoate has fungistatic action and salicylic acid has keratolytic action. So as the infected stratum corneum is shed, it is replaced by healthy skin.

Use

Topical application on skin infected with dermatophytes especially on the foot.

For children one month onwards it can be applied twice daily after cleaning the area, for several months

Ideally skin scrapings should be examined to confirm diagnosis before treatment is begun. For widespread or intractable fungal infections and infections involving nail and hair systemic antifungals are required.

It is listed in WHO guidelines [19].

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

There are not many studies on this drug, but is in use for several years in low income countries, for topical therapy of dermatophyte infections. Available data show that it is effective for this purpose[106-109] and probably for other skin diseases like erythrasma[110].

6. Summary of comparative evidence on safety

Adverse events are rare and include mild irritation at the site of application. It is a popular topical drug in low income countries and is used in children and adults. So lack of reported severe adverse events can be interpreted as that the drug is safe.

7. Summary of available data on comparative cost

It can be made locally from ingredients and so can be very cheap.

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Compared to all other commercial topical applications for ring worm infections, this will be the cheapest drug.

9. Summary of regulatory status

Licensed for use in children.

10. Availability of pharmacopoeial standards

Not available.

11. Proposed text for WHO model formulary

Whitfield's ointment

This is an ointment containing 6% benzoic acid and 3% salicylic acid.

Use

For topical application on localised dermatophyte infections of the skin

Dosage

Apply after cleaning the area, twice daily. Several months' may be required for cure.

Precautions

Do not apply on inflamed areas. May not be effective if nails and hair are involved

Adverse events

No significant adverse events. Irritation at application site can occur.

Gentian violet

Trials summarized in tables

Nyst, 1992

1. Formulation proposed for inclusion

0. 5% - 1% gentian violet in water – available as crystals for making into solutions.

2. International availability (sources)

Gentian violet crystals are available from MEDS, MISSION, IDA, IMRES, DURBIN, JMS, ACTION, ORBI.

3. Whether listing is requested as individual drug or as an example of a therapeutic group

Individual drug.

4. Treatment details(dosage, regimen, duration, references to existing WHO or other guidelines, need for special diagnostic or treatment facilities and skills)

The drug has activity against candida and is used as local application for oral and cutaneous candidiasis in resource poor settings. This drug has been replaced by other drugs in several other areas.

About 2ml is swished in the mouth and can be swallowed

It is listed in WHO guidelines [19].

5. Summary of comparative effectiveness in a variety of clinical settings: Identification of clinical evidence (search strategies, systematic reviews identified, reasons for selection/exclusion of particular data)

There is good in vitro activity against Candida species[111]. Studies show that gentian violet is superior to nystatin for oral candidiasis[26].

6. Summary of comparative evidence on safety

Adverse events are rare and include staining. Oral ulcers are reported. It is used in low income countries in community programmes in children for skin infections [112]. There are no reported serious adverse events.

7. Summary of available data on comparative cost

Cost is US$ 0.0452/gm

8. Comparative cost effectiveness presented as range of cost per routine out come (cost per case, cost per out come etc)

Cheap and available in most low income countries.

9. Summary of regulatory status

The products were approved by FDA but now discontinued.

10. Availability of pharmacopoeial standards
Listed in US pharmacoepoeia.

11. Proposed text for WHO model formulary

Gentian violet
Has action against candida

Use
Topical applications for mild to moderate oral candidiasis
Cutaneous candidiasis
Dosage
For oral candidiasis swish about 2ml in the mouth for 7 days
For skin infections – apply locally
Precautions
The solution is made before dispensing
Adverse events
Staining of tissues and clothes
Minor ulceration in the mouth

Potassium iodide

This is a drug used for sporotrichosis. It is proved to be effective in a randomised trial[113] and remains the main stay in treatment of sporotrichosis [114-116].
It is listed in the complementary list of WHO essential drugs.
Reference standard is listed in US pharmacopoeia.

References

1. Balwierz, W., *[Drugs used in prophylaxis and treatment of fungal infections in immunosuppressed children].* Przegl Lek, 2004. **61 Suppl 2**: p. 89-94.
2. Leibovitz, E., M. Rigaud, S. Chandwani, A. Kaul, M.A. Greco, H. Pollack, R. Lawrence, D. Di John, B. Hanna, K. Krasinski, and et al., *Disseminated fungal infections in children infected with human immunodeficiency virus.* Pediatr Infect Dis J, 1991. **10**(12): p. 888-94.
3. Yasuoka, A., *[Fungal infections in HIV-infected patients].* Nippon Ishinkin Gakkai Zasshi, 2006. **47**(3): p. 161-6.
4. MMWR, *Treating Opportunistic Infections Among HIV-Exposed and Infected Children.* 2004, Recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America, 53 (RR14). p. 1-63.
5. Sun, H.Y., M.Y. Chen, S.M. Hsieh, W.H. Sheng, S.Y. Chang, C.F. Hsiao, C.C. Hung and S.C. Chang, *Changes in the clinical spectrum of opportunistic illnesses in persons with HIV infection in Taiwan in the era of highly active antiretroviral therapy.* Jpn J Infect Dis, 2006. **59**(5): p. 311-6.
6. Pappas, P.G., J.H. Rex, J.D. Sobel, S.G. Filler, W.E. Dismukes, T.J. Walsh and J.E. Edwards, *Guidelines for treatment of candidiasis.* Clin Infect Dis, 2004. **38**(2): p. 161-89.
7. Blyth, C.C., K. Hale, P. Palasanthiran, T.A. O'Brien and M.H. Bennett, *Antifungal therapy in infants and children with proven, probable or suspected invasive fungal infections.* Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD006343., 2007.
8. Reichart, P.A., *Oral manifestations in HIV infection: fungal and bacterial infections, Kaposi's sarcoma.* Med Microbiol Immunol (Berl), 2003. **192**(3): p. 165-9.
9. Samaranayake, L.P., P.L. Fidel, J.R. Naglik, S.P. Sweet, R. Teanpaisan, M.M. Coogan, E. Blignaut and P. Wanzala, *Fungal infections associated with HIV infection.* Oral Dis, 2002. **8 Suppl 2**: p. 151-60.
10. MMWR, *Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age.* 1994, Centre for disease control, 43; RR 12. p. 1-10.
11. Pfaller, M.A. and D.J. Diekema, *Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of Candida.* Clin Microbiol Infect, 2004. **10 Suppl 1**: p. 11-23.
12. *Clinical diagnosis and management of common opportunistic infections in HIV-infected children*. Managemnt of HIV infection and antiretroviral therapy in infants and children. 2007: SEARO, WHO.
13. *Management of opportunistic infections and general symptoms of HIV/ AIDs. Clinical protocol for the WHO European region*. 2006, Regional office Europe, WHO.
14. *Children with HIV/AIDS*, in *Integrated management of chidhood illnesses; Management of the child with a serious infection or severe malnutrition;guidelines for care at the first-referral level in developing countries.* 2000, Department of Child and Adolescent Health and Development, WHO, UNICEF.
15. Kirchner, J.T., *Opportunistic fungal infections in patients with HIV disease: combating cryptococcosis and histoplasmosis.* Postgrad Med, 1996. **99**(6): p. 209-16.
16. Imwidthaya, P. and N. Poungvarin, *Cryptococcosis in AIDS.* Postgrad Med J, 2000. **76**(892): p. 85-8.
17. Saag, M.S., R.J. Graybill, R.A. Larsen, P.G. Pappas, J.R. Perfect, W.G. Powderly, J.D. Sobel and W.E. Dismukes, *Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America.* Clin Infect Dis, 2000. **30**(4): p. 710-8.

18. Sloan, D., S. Dlamini, N. Paul and M. Dedicoat, *Treatment of acute cryptococcal meningitis in HIV-infected adults in resource-limited settings (Protocol).* Cochrane Database of Systematic Reviews, 2006(1, Art. No.: CD005647.).

19. *Assess, classify and manage the child for HIV/AIDS*. 2006: Department of Child and Adolescent Health and Dvelopment, WHO, UNICEF.

20. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Edition*, ed. L.L. Brunton, et al. 2006.

21. Pfizer, *Diflucan.* 2004.

22. Aller, A.I., E. Martin-Mazuelos, F. Lozano, J. Gomez-Mateos, L. Steele-Moore, W.J. Holloway, M.J. Gutierrez, F.J. Recio and A. Espinel-Ingroff, *Correlation of fluconazole MICs with clinical outcome in cryptococcal infection.* Antimicrob Agents Chemother, 2000. **44**(6): p. 1544-8.

23. Testore, G.P., L. Dori, A.R. Buonomini, G.C. Schito, O. Soro, G. Fortina, S. Andreoni, N. Carlone, V. Tullio and M. Andreoni, *In vitro fluconazole susceptibility of 1565 clinical isolates of Candida species evaluated by the disk diffusion method performed using NCCLS M44-A guidelines.* Diagn Microbiol Infect Dis, 2004. **50**(3): p. 187-92.

24. Pfaller, M.A., S.A. Messer, L. Boyken, R.J. Hollis, C. Rice, S. Tendolkar and D.J. Diekema, *In vitro activities of voriconazole, posaconazole, and fluconazole against 4,169 clinical isolates of Candida spp. and Cryptococcus neoformans collected during 2001 and 2002 in the ARTEMIS global antifungal surveillance program.* Diagn Microbiol Infect Dis, 2004. **48**(3): p. 201-5.

25. Sonego-Krone, S., D. Sanchez-Di Martino, R. Ayala-Lugo, G. Torres-Alvariza, C.N. Ta, L. Barbosa and H.M. de Kaspar, *Clinical results of topical fluconazole for the treatment of filamentous fungal keratitis.* Graefes Arch Clin Exp Ophthalmol, 2006. **244**(7): p. 782-7.

26. Pienaar, E.D., T. Young and H. Holmes, *Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children.* Cochrane Database of Systematic Reviews, Issue 3. CD003940., 2006.

27. Flynn, P.M., C.K. Cunningham, T. Kerkering, A.R. San Jorge, V.B. Peters, P.A. Pitel, J. Harris, G. Gilbert, L. Castagnaro and P. Robinson, *Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of orally administered fluconazole suspension versus nystatin. The Multicenter Fluconazole Study Group.* J Pediatr, 1995. **127**(2): p. 322-8.

28. Kontoyiannis, D.P., G.P. Bodey and C.S. Mantzoros, *Fluconazole vs. amphotericin B for the management of candidaemia in adults: a meta-analysis.* Mycoses, 2001. **44**(5): p. 125 -35.

29. Fasano, C., J. O'Keeffe and D. Gibbs, *Fluconazole treatment of neonates and infants with severe fungal infections not treatable with conventional agents.* Eur J Clin Microbiol Infect Dis, 1994. **13**(4): p. 351-4.

30. Schwarze, R., A. Penk and L. Pittrow, *Treatment of candidal infections with fluconazole in neonates and infants.* Eur J Med Res, 2000. **5**(5): p. 203-8.

31. Mondal, R.K., S.C. Singhi, A. Chakrabarti and J. M, *Randomized comparison between fluconazole and itraconazole for the treatment of candidemia in a pediatric intensive care unit: a preliminary study.* Pediatr Crit Care Med, 2004. **5**(6): p. 561-5.

32. Clerihew, L. and W. McGuire, *Systemic antifungal drugs for invasive fungal infection in preterm infants.* Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003953., 2004.

33. McGuire, W., L. Clerihew and N. Austin, *Prophylactic intravenous antifungal agents to prevent mortality and morbidity in very low birth weight infants.* Cochrane Database of Systematic Reviews Issue 1. Art. No.: CD003850, 2004.

34. Chang, L.W., W.T. Phipps, G.E. Kennedy and G.W. Rutherford, *Antifungal interventions for the primary prevention of cryptococcal disease in adults with HIV.* Cochrane Database of Systematic Reviews, 2005(3. CD004773).

35. Mootsikapun, P., P. Chetchotisakd, S. Anunnatsiri and K. Choksawadphinyo, *The efficacy of fluconazole 600 mg/day versus itraconazole 600 mg/day as consolidation therapy of cryptococcal meningitis in AIDS patients.* J Med Assoc Thai, 2003. **86**(4): p. 293-8.

36. Saag, M.S., G.A. Cloud, J.R. Graybill, J.D. Sobel, C.U. Tuazon, P.C. Johnson, W.J. Fessel, B.L. Moskovitz, B. Wiesinger, D. Cosmatos, L. Riser, C. Thomas, R. Hafner, and W.E. Dismukes, *A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group.* Clin Infect Dis, 1999. **28**(2): p. 291-6.

37. Ehninger, G., H.K. Schuler and E. Sarnow, *Fluconazole in the prophylaxis of fungal infection after bone marrow transplantation.* Mycoses, 1996. **39**(7-8): p. 259-63.

38. Foster, K.W., S.F. Friedlander, H. Panzer, M.A. Ghannoum and B.E. Elewski, *A randomized controlled trial assessing the efficacy of fluconazole in the treatment of pediatric tinea capitis.* J Am Acad Dermatol, 2005. **53**(5): p. 798-809.

39. Johansen, H.K. and P.C. Gotzsche, *Amphotericin B versus fluconazole for controlling fungal infections in neutropenic cancer patients.* Cochrane Database Syst Rev, 2002(2): p. CD000239.

40. Girois, S.B., F. Chapuis, E. Decullier and B.G. Revol, *Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis.* Eur J Clin Microbiol Infect Dis, 2005. **24**(2): p. 119-30.

41. de Repentigny, L., J. Ratelle, J.M. Leclerc, G. Cornu, E.M. Sokal, P. Jacqmin and K. De Beule, *Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children.* Antimicrob Agents Chemother, 1998. **42**(2): p. 404-8.

42. Phillips, P., J. Zemcov, W. Mahmood, J.S. Montaner, K. Craib and A.M. Clarke, *Itraconazole cyclodextrin solution for fluconazole-refractory oropharyngeal candidiasis in AIDS: correlation of clinical response with in vitro susceptibility.* Aids, 1996. **10**(12): p. 1369-76.

43. Wilcox, C.M., R.O. Darouiche, L. Laine, B.L. Moskovitz, I. Mallegol and J. Wu, *A randomized, double-blind comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis.* J Infect Dis, 1997. **176**(1): p. 227-32.

44. Aanpreung, P. and G. Veerakul, *Itraconazole for treatment of oral candidosis in pediatric cancer patients.* J Med Assoc Thai, 1997. **80**(6): p. 358-62.

45. Groll, A.H., L. Wood, M. Roden, D. Mickiene, C.C. Chiou, E. Townley, L. Dad, S.C. Piscitelli and T.J. Walsh, *Safety, pharmacokinetics, and pharmacodynamics of cyclodextrin itraconazole in pediatric patients with oropharyngeal candidiasis.* Antimicrob Agents Chemother, 2002. **46**(8): p. 2554-63.

46. Koumantaki-Mathioudaki, E., D. Devliotou-Panagiotidou, E. Rallis, V. Athanassopoulou, T. Koussidou-Eremondi, A. Katsambas and E. Frangoulis, *Is itraconazole the treatment of choice in Microsporum canis tinea capitis?* Drugs Exp Clin Res, 2005. **31 Suppl**: p. 11-5.

47. Gupta, A.K., S. Nolting, Y. de Prost, J. Delescluse, H. Degreef, U. Theissen, R. Wallace, G. Marynissen and P. De Doncker, *The use of itraconazole to treat cutaneous fungal infections in children.* Dermatology, 1999. **199**(3): p. 248-52.

48. Lopez-Gomez, S., A. Del Palacio, J. Van Cutsem, M. Soledad Cuetara, L. Iglesias and A. Rodriguez-Noriega, *Itraconazole versus griseofulvin in the treatment of tinea capitis: a double-blind randomized study in children.* Int J Dermatol, 1994. **33**(10): p. 743-7.

49. Degreef, H., *Itraconazole in the treatment of tinea capitis.* Cutis, 1996. **58**(1): p. 90-3.

50. Crawford, F., P. Young, C. Godfrey, S.E. Bell-Syer, R. Hart, E. Brunt and I. Russell, *Oral treatments for toenail onychomycosis: a systematic review.* Arch Dermatol, 2002. **138**(6): p. 811-6.

51. Bell-Syer, S.E., R. Hart, F. Crawford, D.J. Torgerson, W. Tyrrell and I. Russell, *Oral treatments for fungal infections of the skin of the foot.* Cochrane Database Syst Rev, 2002(2): p. CD003584.

52. Wingfield, A.B., A.C. Fernandez-Obregon, F.S. Wignall and D.L. Greer, *Treatment of tinea imbricata: a randomized clinical trial using griseofulvin, terbinafine, itraconazole and fluconazole.* Br J Dermatol, 2004. **150**(1): p. 119-26.

53. Wheat, J., R. Hafner, A.H. Korzun, M.T. Limjoco, P. Spencer, R.A. Larsen, F.M. Hecht and W. Powderly, *Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group.* Am J Med, 1995. **98**(4): p. 336-42.

54. Tobon, A.M., L. Franco, D. Espinal, I. Gomez, M. Arango, H. Trujillo and A. Restrepo, *Disseminated histoplasmosis in children: the role of itraconazole therapy.* Pediatr Infect Dis J, 1996. **15**(11): p. 1002-8.

55. Baley, J.E., C. Meyers, R.M. Kliegman, M.R. Jacobs and J.L. Blumer, *Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates.* J Pediatr, 1990. **116**(5): p. 791-7.

56. Viscoli, C., E. Castagnola, M.T. Van Lint, C. Moroni, A. Garaventa, M.R. Rossi, R. Fanci, F. Menichetti, D. Caselli, M. Giacchino, and M. Congiu, *Fluconazole versus amphotericin B as empirical antifungal therapy of unexplained fever in granulocytopenic cancer patients: a pragmatic, multicentre, prospective and randomised clinical trial.* Eur J Cancer, 1996. **32A**(5): p. 814-20.

57. Brouwer, A.E., A. Rajanuwong, W. Chierakul, G.E. Griffin, R.A. Larsen, N.J. White and T.S. Harrison, *Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial.* Lancet, 2004. **363**(9423): p. 1764-7.

58. Driessen, M., J.B. Ellis, P.A. Cooper, S. Wainer, F. Muwazi, D. Hahn, H. Gous and F.P. De Villiers, *Fluconazole vs. amphotericin B for the treatment of neonatal fungal septicemia: a prospective randomized trial.* Pediatr Infect Dis J, 1996. **15**(12): p. 1107-12.

59. Nath, C.E., A.J. McLachlan, P.J. Shaw, J.C. Coakley and J.W. Earl, *Amphotericin B Dose Optimization in Children with Malignant Diseases.* Chemotherapy, 2007. **53**(2): p. 142-147.

60. Benson, J.M. and M.C. Nahata, *Pharmacokinetics of amphotericin B in children.* Antimicrob Agents Chemother, 1989. **33**(11): p. 1989-93.

61. Starke, J.R., E.O. Mason, Jr., W.G. Kramer and S.L. Kaplan, *Pharmacokinetics of amphotericin B in infants and children.* J Infect Dis, 1987. **155**(4): p. 766-74.

62. Wiley, J.M., N.L. Seibel and T.J. Walsh, *Efficacy and safety of amphotericin B lipid complex in 548 children and adolescents with invasive fungal infections.* Pediatr Infect Dis J, 2005. **24**(2): p. 167-74.

63. Koren, G., A. Lau, J. Klein, C. Golas, M. Bologa-Campeanu, S. Soldin, S.M. MacLeod and C. Prober, *Pharmacokinetics and adverse effects of amphotericin B in infants and children.* J Pediatr, 1988. **113**(3): p. 559-63.

64. Kaur, R., D. Rawat, M. Kakkar, R. Monga and V.K. Sharma, *Cryptococcal meningitis in pediatric AIDS.* J Trop Pediatr, 2003. **49**(2): p. 124-5.

65. Leggiadro, R.J., M.W. Kline and W.T. Hughes, *Extrapulmonary cryptococcosis in children with acquired immunodeficiency syndrome.* Pediatr Infect Dis J, 1991. **10**(9): p. 658-62.

66. Brouwer, A.E., H.J. van Kan, E. Johnson, A. Rajanuwong, P. Teparrukkul, V. Wuthiekanun, W. Chierakul, N. Day and T.S. Harrison, *Oral versus intravenous flucytosine in patients with HIV-associated cryptococcal meningitis.* Antimicrob Agents Chemother, 2006.

67. Soltani, M., C.M. Tobin, K.E. Bowker, J. Sunderland, A.P. MacGowan and A.M. Lovering, *Evidence of excessive concentrations of 5-flucytosine in children aged below 12 years: a 12-year review*

of serum concentrations from a UK clinical assay reference laboratory. Int J Antimicrob Agents, 2006. **28**(6): p. 574-7.

68. Posteraro, B., M. Sanguinetti, B. Fiori, M. La Sorda, T. Spanu, D. Sanglard and G. Fadda, *Caspofungin activity against clinical isolates of azole cross-resistant Candida glabrata overexpressing efflux pump genes.* J Antimicrob Chemother, 2006. **58**(2): p. 458-61.

69. Deresinski, S.C. and D.A. Stevens, *Caspofungin.* Clin Infect Dis, 2003. **36**(11): p. 1445-57.

70. Stone, J.A., E.M. Migoya, L. Hickey, G.A. Winchell, P.J. Deutsch, K. Ghosh, A. Freeman, S. Bi, R. Desai, S.C. Dilzer, K.C. Lasseter, W.K. Kraft, H. Greenberg, and S.A. Waldman, *Potential for interactions between caspofungin and nelfinavir or rifampin.* Antimicrob Agents Chemother, 2004. **48**(11): p. 4306-14.

71. Aoun, M., *Clinical efficacy of caspofungin in the treatment of invasive aspergillosis.* Med Mycol, 2006. **44 Suppl**: p. 363-6.

72. Walsh, T.J., P.C. Adamson, N.L. Seibel, P.M. Flynn, M.N. Neely, C. Schwartz, A. Shad, S.L. Kaplan, M.M. Roden, J.A. Stone, A. Miller, S.K. Bradshaw, S.X. Li, C.A. Sable, and N.A. Kartsonis, *Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents.* Antimicrob Agents Chemother, 2005. **49**(11): p. 4536-45.

73. Groll, A.H. and J. Ritter, *[Diagnosis and management of fungal infections and pneumocystis pneumonitis in pediatric cancer patients].* Klin Padiatr, 2005. **217 Suppl 1**: p. S37-66.

74. Mora-Duarte, J., R. Betts, C. Rotstein, A.L. Colombo, L. Thompson-Moya, J. Smietana, R. Lupinacci, C. Sable, N. Kartsonis and J. Perfect, *Comparison of caspofungin and amphotericin B for invasive candidiasis.* N Engl J Med, 2002. **347**(25): p. 2020-9.

75. Colombo, A.L., J. Perfect, M. DiNubile, K. Bartizal, M. Motyl, P. Hicks, R. Lupinacci, C. Sable and N. Kartsonis, *Global distribution and outcomes for Candida species causing invasive candidiasis: results from an international randomized double-blind study of caspofungin versus amphotericin B for the treatment of invasive candidiasis.* Eur J Clin Microbiol Infect Dis, 2003. **22**(8): p. 470-4.

76. Arathoon, E.G., E. Gotuzzo, L.M. Noriega, R.S. Berman, M.J. DiNubile and C.A. Sable, *Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiases.* Antimicrob Agents Chemother, 2002. **46**(2): p. 451-7.

77. Kartsonis, N., M.J. DiNubile, K. Bartizal, P.S. Hicks, D. Ryan and C.A. Sable, *Efficacy of caspofungin in the treatment of esophageal candidiasis resistant to fluconazole.* J Acquir Immune Defic Syndr, 2002. **31**(2): p. 183-7.

78. Kartsonis, N.A., A. Saah, C.J. Lipka, A. Taylor and C.A. Sable, *Second-line therapy with caspofungin for mucosal or invasive candidiasis: results from the caspofungin compassionate-use study.* J Antimicrob Chemother, 2004. **53**(5): p. 878-81.

79. Villanueva, A., E. Gotuzzo, E.G. Arathoon, L.M. Noriega, N.A. Kartsonis, R.J. Lupinacci, J.M. Smietana, M.J. DiNubile and C.A. Sable, *A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis.* Am J Med, 2002. **113**(4): p. 294-9.

80. Villanueva, A., E.G. Arathoon, E. Gotuzzo, R.S. Berman, M.J. DiNubile and C.A. Sable, *A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis.* Clin Infect Dis, 2001. **33**(9): p. 1529-35.

81. Betts, R., A. Glasmacher, J. Maertens, G. Maschmeyer, J.A. Vazquez, H. Teppler, A. Taylor, R. Lupinacci, C. Sable and N. Kartsonis, *Efficacy of caspofungin against invasive Candida or invasive Aspergillus infections in neutropenic patients.* Cancer, 2006. **106**(2): p. 466-73.

82. Stone, E.A., H.B. Fung and H.L. Kirschenbaum, *Caspofungin: an echinocandin antifungal agent.* Clin Ther, 2002. **24**(3): p. 351-77; discussion 329.

83. Merlin, E., C. Galambrun, P. Ribaud, T. Blanc, G. Michel, A. Auvrignon and J.L. Stephan, *Efficacy and safety of caspofungin therapy in children with invasive fungal infections.* Pediatr Infect Dis J, 2006. **25**(12): p. 1186-8.

84. Pancham, S., C. Hemmaway, H. New, E. Albert, I. Dokal, I.A. Roberts and M. McCloy, *Caspofungin for invasive fungal infections: combination treatment with liposomal amphotericin B in children undergoing hemopoietic stem cell transplantation.* Pediatr Transplant, 2005. **9**(2): p. 254-7.

85. Franklin, J.A., J. McCormick and P.M. Flynn, *Retrospective study of the safety of caspofungin in immunocompromised pediatric patients.* Pediatr Infect Dis J, 2003. **22**(8): p. 747-9.

86. Fleece, D., J.P. Gaughan and S.C. Aronoff, *Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials.* Pediatrics, 2004. **114**(5): p. 1312-5.

87. Aste, N. and M. Pau, *Tinea capitis caused by Microsporum canis treated with terbinafine.* Mycoses, 2004. **47**(9-10): p. 428-30.

88. Devliotou-Panagiotidou, D. and T.H. Koussidou-Eremondi, *Efficacy and tolerability of 8 weeks' treatment with terbinafine in children with tinea capitis caused by Microsporum canis: a comparison of three doses.* J Eur Acad Dermatol Venereol, 2004. **18**(2): p. 155-9.

89. Lipozencic, J., M. Skerlev, R. Orofino-Costa, V.C. Zaitz, A. Horvath, E. Chouela, G. Romero, N. Gourmala and C. Paul, *A randomized, double-blind, parallel-group, duration-finding study of oral terbinafine and open-label, high-dose griseofulvin in children with tinea capitis due to Microsporum species.* Br J Dermatol, 2002. **146**(5): p. 816-23.

90. Wen, J. and Z.F. Lin, *[Effect of terbinafine in treating onychomycosis in children: clinical observation of 88 cases].* Di Yi Jun Yi Da Xue Xue Bao, 2005. **25**(5): p. 582-3.

91. Gupta, A.K., J.E. Ryder, L.E. Lynch and A. Tavakkol, *The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence.* J Drugs Dermatol, 2005. **4**(3): p. 302-8.

92. Warshaw, E.M., D.D. Fett, H.E. Bloomfield, J.P. Grill, D.B. Nelson, V. Quintero, S.M. Carver, G.R. Zielke and F.A. Lederle, *Pulse versus continuous terbinafine for onychomycosis: a randomized, double-blind, controlled trial.* J Am Acad Dermatol, 2005. **53**(4): p. 578-84.

93. Haroon, T.S., I. Hussain, A. Mahmood, A.H. Nagi, I. Ahmad and M. Zahid, *An open clinical pilot study of the efficacy and safety of oral terbinafine in dry non-inflammatory tinea capitis.* Br J Dermatol, 1992. **126 Suppl 39**: p. 47-50.

94. Rich, P., K.R. Houpt, A. LaMarca, K.H. Loven, T.C. Marbury, R. Matheson, B. Miller, S. Smith and J. Wolf, *Safety and efficacy of short-duration oral terbinafine for the treatment of tinea corporis or tinea cruris in subjects with HIV infection or diabetes.* Cutis, 2001. **68**(1 Suppl): p. 15-22.

95. Smith, S., K. Houpt, P. Rich, A. LaMarca, J.M. Weinberg, T.S. Alferez, E. Atillasoy and C. Opper, *Short-duration oral terbinafine for the treatment of tinea pedis in HIV-positive patients.* Cutis, 2001. **68**(1 Suppl): p. 30-9.

96. Bakos, L., A.C. Brito, L.C. Castro, B. Gontijo, G. Lowy, C.M. Reis, A.M. Ribeiro, F.H. Souza, L. Villar Mdo and C. Zaitz, *Open clinical study of the efficacy and safety of terbinafine cream 1% in children with tinea corporis and tinea cruris.* Pediatr Infect Dis J, 1997. **16**(6): p. 545-8.

97. Schopf, R., O. Hettler, M. Brautigam, G. Weidinger, U. Kaben, P. Mayser and V. Resl, *Efficacy and tolerability of terbinafine 1% topical solution used for 1 week compared with 4 weeks clotrimazole 1% topical solution in the treatment of interdigital tinea pedis: a randomized, double-blind, multi-centre, 8-week clinical trial.* Mycoses, 1999. **42**(5-6): p. 415-20.

98. Aguilar, C. and K.K. Mueller, *Reversible agranulocytosis associated with oral terbinafine in a pediatric patient.* J Am Acad Dermatol, 2001. **45**(4): p. 632-4.

99. Mendling, W., C. Krauss and B. Fladung, *A clinical multicenter study comparing efficacy and tolerability of topical combination therapy with clotrimazole (Canesten, two formats) with oral single dose fluconazole (Diflucan) in vulvovaginal mycoses.* Mycoses, 2004. **47**(3-4): p. 136-42.

100. Binet, O., J. Soto-Melo, J. Delgadillo, S. Videla, I. Izquierdo and J. Forn, *Flutrimazole 1% dermal cream in the treatment of dermatomycoses: a randomized, multicentre, double-blind, comparative clinical trial with 1% clotrimazole cream. Flutrimazole Study Group.* Mycoses, 1994. **37**(11-12): p. 455-9.

101. Emele, F.E., A.A. Fadahunsi, C.E. Anyiwo and O. Ogunleye, *A comparative clinical evaluation of econazole nitrate, miconazole, and nystatin in the treatment of vaginal candidiasis.* West Afr J Med, 2000. **19**(1): p. 12-5.

102. Repiso Montero, T., S. Lopez, C. Rodriguez, R. del Rio, A. Badell and M.R. Gratacos, *Eberconazole 1% cream is an effective and safe alternative for dermatophytosis treatment: multicenter, randomized, double-blind, comparative trial with miconazole 2% cream.* Int J Dermatol, 2006. **45**(5): p. 600-4.

103. Concannon, P., E. Gisoldi, S. Phillips and R. Grossman, *Diaper dermatitis: a therapeutic dilemma. Results of a double-blind placebo controlled trial of miconazole nitrate 0.25%.* Pediatr Dermatol, 2001. **18**(2): p. 149-55.

104. Dhondt, F., J. Ninane, K. De Beule, A. Dhondt and G. Cauwenbergh, *Oral candidosis: treatment with absorbable and non-absorbable antifungal agents in children.* Mycoses, 1992. **35**(1-2): p. 1-8.

105. Groll, A.H., G. Just-Nuebling, M. Kurz, C. Mueller, U. Nowak-Goettl, D. Schwabe, P.M. Shah and B. Kornhuber, *Fluconazole versus nystatin in the prevention of candida infections in children and adolescents undergoing remission induction or consolidation chemotherapy for cancer.* J Antimicrob Chemother, 1997. **40**(6): p. 855-62.

106. Ponnighaus, J.M., V. Gooskens, Y. Clayton, P. Mkandawire and J. Sterne, *[Treatment of superficial mycoses in the tropics. Results of a double-blind study in the Karonga District, Malawi].* Mycoses, 1994. **37 Suppl 1**: p. 101-4.

107. Logan, R.A., R.J. Hay and M. Whitefield, *Antifungal efficacy of a combination of benzoic and salicylic acids in a novel aqueous vanishing cream formulation.* J Am Acad Dermatol, 1987. **16**(1 Pt 1): p. 136-8.

108. Schmeller, W., *Community health workers reduce skin diseases in East African children.* Int J Dermatol, 1998. **37**(5): p. 370-7.

109. Gooskens, V., J.M. Ponnighaus, Y. Clayton, P. Mkandawire and J.A. Sterne, *Treatment of superficial mycoses in the tropics: Whitfield's ointment versus clotrimazole.* Int J Dermatol, 1994. **33**(10): p. 738-42.

110. Holdiness, M.R., *Management of cutaneous erythrasma.* Drugs, 2002. **62**(8): p. 1131-41.

111. Kondo, S., T. Yamada, N. Satoh, K. Saionji, T. Oguri and J. Igari, *[In vitro activity of methylrosaniline chloride (gentian violet) as disinfectant against Candida spp. and Trichosporon spp. isolated from blood samples].* Kansenshogaku Zasshi, 2006. **80**(6): p. 651-5.

112. Schmeller, W. and A. Dzikus, *Skin diseases in children in rural Kenya: long-term results of a dermatology project within the primary health care system.* Br J Dermatol, 2001. **144**(1): p. 118-24.

113. Cabezas, C., B. Bustamante, W. Holgado and R.E. Begue, *Treatment of cutaneous sporotrichosis with one daily dose of potassium iodide.* Pediatr Infect Dis J, 1996. **15**(4): p. 352-4.

114. Coskun, B., Y. Saral, N. Akpolat, A. Ataseven and D. Cicek, *Sporotrichosis successfully treated with terbinafine and potassium iodide: case report and review of the literature.* Mycopathologia, 2004. **158**(1): p. 53-6.

115. Sandhu, K. and S. Gupta, *Potassium iodide remains the most effective therapy for cutaneous sporotrichosis.* J Dermatolog Treat, 2003. **14**(4): p. 200-2.

116. Sterling, J.B. and W.R. Heymann, *Potassium iodide in dermatology: a 19th century drug for the 21st century-uses, pharmacology, adverse effects, and contraindications.* J Am Acad Dermatol, 2000. **43**(4): p. 691-7.

Table 1 -Antifungal drugs for preventing and treating oropharyngeal (OPC) candidiasis [1]

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome	Adverse events
Arathoon 2002 South America 18 centres Allocation concealment : B	Random, double blind, no ITT	OPC/ Oesophageal	C1 - caspofungin acetate 35 mg (34) C2 - caspofungin acetate 50 mg (34) C3 - caspofungin acetate 70 mg plus placebo (37) A1 - amphotericin B (0,5mg/kg) or placebo intravenously, once daily (35) Duration: 7-14 days	Clinical and Microbiological cure within 3-4 days after discontinuing therapy Relapse	Significantly fewer caspofungin recipients had drug-related fever, chills, nausea or vomiting. Local reactions (infusion related) ranged from 6-14% across treatment arms. Drug related lab abnormalities (raised ALT, AST, ALP, Creatinine, and decreased K) were more common in amphotericin B.
Chavenet 1992 France Allocation concealment: A	Random Not blinded No ITT	Oral candidiasis, 18y or older, HIV pos	1. Amphotericin deoxycholate dissolved in either: 5% glucose - final concentration 1.6 g amphotericin / l (11) 2. Parenteral amphotericin fat emulsion - final concentration 2 g amphotericin / l (11) Given as a 1 hour infusion of 1mg/kg/day on four consecutive days	Clinical and microbiological cure	More frequent with glucose preparation. Chills and fever were most frequent side effect - 66% vs 4%. Sweating and Nausea slightly less frequent in Fat emulsion group.
De Wit 1989 Belgium Allocation concealment : B unclear	Random, Patients blinded, No ITT	OPC 18y or older AIDS/ARC	50mg fluconazole once daily (18) 200mg ketoconazole once daily (19) Duration: 28 days	Clinical and microbiological cure Relapse	severe nausea in 1 fluconazole patient, transient rise (< 3 times baseline) ALT or AST in 1 fluconazole and 4 ketoconazole patient
De Wit 1993 Belgium Allocation concealment : B unclear	Random, not blinded, no ITT	OPC 18y or older AIDS/ARC	50mg fluconazole once daily for 7 days (28) 150mg fluconazole as a single dose (28) Duration: 7 days; monitored 26 patients (13/group) for 2 weeks after treatment	Clinical and microbiological cure Relapse	None reported

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome	Adverse events
De wit 1997 Brussels, London, Manchester, Paris Allocation concealment : A	Random, double blind, noITT	OPC with or without oesophageal 18y -62y HIV pos	D1 - D0870 100mg initial dose followed by 25 mg/day for 4 days (13) D2 - D0870 10mg once daily for 5 days (14)	Clinical cure Relapse after 7 -14 days	1 patient had dizziness (D1) another had diarrhoea (D2).
De wit 1998 Belgium Allocation concealment : B	Random Open label No ITT	OPC 16y – 65y AIDS/ARC	Fluconazole - 150 mg stat (20) Itraconazole - 100 mg daily for 7 days (20)	Clinical cure Mycological cure Relapse	None reported
Graybill 1998 USA 12 centre Allocation concealment : C inadequate	Random Open label No ITT	OPC >13yrs HIV pos	1. Itraconazole oral solutions 200mg/day for 7 days (64) 2. 200mg/day for 14 days (64) 3. Fluconazole tablets 200mg on day 1, 100mg daily for the remaining 13 days (62)	Clinical cure Mycological cure Relapse	25% each treatment arm GIT adverse events. Respiratory side effects 21% fluconazole, 12.5% itraconazole.
Hernandez 1994 Spain – multicentric Allocation concealment : C inadequate	Random Open label No ITT	OPC 7wks- 14y HIV pos	1. Fluconazole oral suspension once daily; 3mg/kg body weight for 23 pts and 2mg/kg for 1. Mean dur 14 d (24) 2. Ketaconazole oral suspension: once daily; 7mg/kg body weight in 19 pts and 3,5mg/kg for 3. Mean duration 16d (22)	Clinical response Mycological cure Relapse	GIT toxicity - 1 patient ketoconazole group (diarrhoea and abdominal pain). Two patients also had increased ALT and AST vs 1 in fluconazole. 1 in latter group had thrombocytopaenia
Just Nubling 1991 Germany Allocation concealment : A	Random No blinding No ITT	Advanced HIV infection Candidiasis in previous 3 m. No present candidiasis	1 - no treatment (22) 2 - 50mg fluconazole daily (21) 3 - 100mg fluconazole daily (22)	Relapse Adverse effects	Allergic exanthema in fluconazole group
Leen 1990 UK Allocation concealment : B unclear	Random Patient blinded ITT	OPC HIV pos men 18-65y Maintenance after cure with flucnazole	Fluconazole 150mg weekly (9) Placebo (5) Duration: 24 weeks	Relapse Adverse effects	One on Fluconazole developed diarrhoea

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome	Adverse events
Linpiyawan 2000 Thailand Allocation concealment : B unclear	Random Observer blind ITT	OPC AIDS	Clotrimazole troche 10mg five time daily (15) Itraconazole oral soln 100mg/10ml twice daily (14) Duration: 1 week	Clinical cure Mycological cure	Two patients developed elevated liver enzymes
MC Phail 1996 USA Allocation concealment : B unclear	Random Double blind No ITT	HIV/AIDS No OC =58 Cured OC =70	Within each strata 1. 2 placebo pastilles daily 2.One nystatin (200,000 U) and 1 placebo pastille daily 3.Two nystatin pastilles daily Duration: 20 weeks	Delay in onset of OC	
Marriott, 1993 Australia Allocation concealment : B unclear	Random, Patient blind ITT	HIV Male >18yrs OPC cured with fluconazole	Weekly dose of 1. 150mg Fluconazole (44) 2. Placebo (40) for 24 weeks	Clinical recurrence	Fluconazole - 40 intercurrent illnesses, 9 adverse drug reactions, 3 deaths Placebo - 5 intercurrent illnesses, 1 adverse drug reaction and 2 deaths.
Mc Kinsey, 1999 USA, multicentre Allocation concealment : B unclear	Random Patient blind ITT	HIV pos >13yrs Life expect >1yr No active fungal infect Resident in Histoplasma area	1. Itraconazole 2 x 100mg capsules daily for 32 months (149) 2. Placebo (146)	Prevention of histoplasmosis Prevenion of recurrence of other fungal infections	diarrhoea, abdominal pain, nausea, vomiting, elevated liver enzymes, rash and Stevens-Johnson syndrome
Murray 1997 USA multicentre Allocation concealment : B unclear	Random Investigator blind No ITT	OPC Immunocompromised (HIV/others) >13yrs HIV (123)	1. Itraconazole oral solution: once each day two 10mL aliquots swished vigorously in the mouth for several seconds and then swallowed (61) 2. Clotrimazole troches: 5 daily, dissolved slowly in the mouth (62) Duration: 14 days. If cured observed for 1 month	Cure Recurrence	GIT symptoms mainly. 7 patients in ictraconazole group and 3 in clotrimazole group had to discontinue study participation prematurely as a result of adverse events.

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome	Adverse events
Nyst, 1992 Zaire Allocation concealment : A	Random Not blinded No ITT	OPC adults	1. Gentian violet - mouth wash 0.5% aqueous solution 1.5ml bd; wash for 2 minutes, swallow (49) 2. Ketoconazole - 200mg/day (45) 3. Nystatin - mouth wash suspension 200.000 U qid; wash 2 min and swallow (47) Duration: 10 d or till no symptom.	Clinical cure	2 patients receiving gentian violet developed irritation and small superficial ulcers of the oral mucosa 24 hours of start of therapy
Pagani, 2002 Switzerland Allocation concealment : B unclear	Random Double bind No ITT	HIV pos OPC cured with Fluconazole >16yrs	1 Fluconazole 150mg weekly (71) 2. Placebo weekly (72) Duration: 7 - 14 days; planned follow-up 18 months	Third relapse of OPC, dev of mycol resistance to fluconazole in association with clin resistance.	No drop out because of adverse reactions
Phillips, 1998 Austria; Belgium; Canada: Germany; Netherlands; Spain; UK Allocation concealment :B	Random Double blind No ITT	HIV pos >19yrs Had OPC	1.Fluconazole capsules (100mg OD for 14d) + placebo oral solution (86) 2. Itraconazole oral solution 100mg OD for 14d + placebo capsules (79) 3. Itraconazole oral solution 100mg bd for 7 d + placebo capsules (79)	Clinical cure Mycological cure Relapse	GIT (nausea, vomitimg, abdominal pain, anorexia and liver enzyme abnormalities), rash, fever, neurological (headache, coma, convulsions and hemiparesis) hypotension, 1 death in fluconazole arm
Pons, 1993 USA multicentre Allocation concealment : B	Random Clinician blinded ITT	OPC >17yrs AIDS	1. Fluconazole - 100 mg once daily for 14 days (176) 2. Clotrimazole - 10 mg five times daily for 14 days (158)	Clinical cure Mycological cure Relapse	GIT most common headache, dizziness, pruritus, rash, sweating and dry mouth liver function abnormalities
Pons,1997 USA multicentre Allocation concealment : B unclear	Random Clinician blinded No ITT	OPC HIV/AIDS	1. Fluconazole - 200mg loading dose then 100mg once daily for 14 d (83) 2. Nystatin -500,000 U four times daily for 14 d (84) Follow up - after 28 and 48 days	Clinical cure Mycological cure	GIT
Redding, 1992 USA Allocation concealment :	Random Clinician blinded ITT	HIV pos Adults Thrush	1. Fluconazole 100mg tablets OD for 14 d (13) 2. Clotrimazole 10mg troches five times per day for 14 d (11)	Clinical cure Mycology Relapse	Nausea Flatulence

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome	Adverse events
B unclear			Clinically cured followed at d28, d42		
Revanker, 1998 USA Allocation concealment : C indequate	Random, open label No ITT	OPC HIV pos advanced	All treated with 200mg fluconazole on day 1 and 100mg/day for 4 days or until complete clinical response followed by Fluconazole 1.Intermittent - only during relapses of Candidiasis (42) 2.Continuous 200mg/day (20)	Clinical response Mycology Relapse Increase in MIC	-
Schuman, 1997 USA, multicentre Allocation concealment : B	Random Patient and committee blind	Female Advanced HIV, >13yrs	1. Fluconazole 200mg / week (162) 2. Placebo (161)	Preventing candidiasis	-
Smith, 1991 UK Allocation concealment :A	Random, Double blind No ITT	OC HIV pos Homosexual men	1. Itraconazole - 200mg daily plus placebo ketoconazole (59) 2. Ketoconazole - 200mg twice a day plus placebo itraconazole (52) Duration treatment: 28 days	Clinical response Mycology Relapse	5 had to stop ketoconazole due to serious events - 2 nausea, 2 hepatic and 1 generalized erythematous rash. 1on itraconazole developed a maculopapular rash.
Stevens, 1991 USA Allocation concealment : B	Random Blinded ITT	≥18yrs AIDS/ARC Previous thrush	1. Fluconazole 100mg tab OD (12) 2. Placebo once daily (13) Duration: 12 weeks	Relapse	increased liver function tests, GIT symptoms.
Van Roey, 2004 Uganda Allocation concealment : B	Random, Not blinded No ITT	OPC >18yrs Presumed HIV pos	1. Ketoconazole 400mg daily (179) 2. Miconazole nitrate 10mg daily (178) Duration: 7 - 14 days	Clinical cure Relapse	Seen with miconazole

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome	Adverse events
De Repentigny,1996 Canada, Multicentre Allocation concealment : B	Random, Double blind, No ITT	OPC/oesophagi al ≥16yrs HIV pos	1. Itraconazole: two 100mg capsules plus one ketoconazole placebo tablet daily (51) 2. Ketoconazole: one 200mg tablet plus two ictraconazole placebo capsules daily (55) Treatment duration: 2 weeks Cured patients followed up for 6 w	Clinical cure Mycoloy Relapse	No significant differences between treatment groups. Nausea, headache, rash, diarrhoea and taste perversion.

Table 2 Cochrane reviews on preterm infants [2, 3]

Author, Centre	Design	Subjects	Intervention	Outcome	Adverse events
Dreissen,1996 West Africa A	Randomised blinding only for randomisation	22 preterm infants less than 3m old with invasive fungal infection	1.Fluconazole 10mg/kg IV or orally then 5mg/kg once daily (10) 2.Amphotericin B 1mg/kg/day IV (10) Treatment continued until no evidence of infection.	Death before discharge (3 in gr 1 and 4 in gr 2) Adverse events	None that required stopping therapy Thrombophlebiis- 1 and 5 in gr 1 and 2 Vomiting – 1 in gr 1 Liver enz – no sig diff
Cabrera, 2002 Georgia, Augusta A	Randomised, blinded	11 infants birthweight l< 1500 g with fungal colonisation demonstrated on rectal, oro-pharyngeal, or tracheal weekly surveillance cultures	1. Fluconazole 6 mg / kg body weight (6), 2. placebo (N=5). The dosage interval is not known.	Invasive fungal infection	
Kaufman, 2001 Charlottesville A	Randomised Blinded	100 infants <5d old, birthweight < 1000 g. Infants with evidence of liver failure were not eligible for inclusion	1.Fluconazole 3 mg / kg every third day for 2w, then every second day for 3rd and 4th w, then daily during 5,6w (50) 2.Normal saline placebo (50). Assigned to intervention for six weeks, or until IV discontinued.	Colonisation or invasive fungal infection Death before discharge	
Kicklighter 2001 South Carolina	Randomised Blinded	103 infants <3d old, birthweight < 1500 g. Infants with liver failure, congenital heart disease, or congenital defects needing surgery were not eligible for inclusion	1.Fluconazole 6 mg / kg every third day for 1week, then daily upto 4w (50) 2. normal saline placebo (50). Assigned to intervention for four weeks. Administered intravenously and then oro-gastrically	Colonisation or invasive fungal infection Death before discharge	

Table 3: Prevention of Cryptococcal disease in adults with HIV[4]

Author, Centre	Design	Patients	Interventions (no: of patients)	Outcome
Chariyalertsak, 2002 Thailand A	Randomised, double blind controlled ITT	CD4 counts<200	Itraconazole Placebo 129	Invasive fungal infection
Chetchotisakd, 2004 Thailand multicentre B	Randomised, double blind, controlled ITT	CD 4 counts<100	Fluconazole Placebo 90	Cryptococcal infection Death
Mc Kinsey, 1999 USA, multicentre Allocation concealment : B unclear	Randomised patient blind controlled ITT	CD 4 counts <150	Itraconazole Placebo 295	Histoplasmosis Recurrence of other fungal infections
Powderely,1995 USA A	Randomised, open label, ITT	CD4 counts <200	Fluconazole (200 mg daily) Clotrimazole troches (10 mg five times daily 428	Invasive fungal infections Death
Smith, 2001 Multicountry A	Randomised, double blind, controlled	CD4 counts <300	Itraconazole 200mg daily Placebo	Invasive fungal infetion

Table 4 Results of other metaanalyses

	Purpose	Studies	Outcome
Kontoyiannis D P,2001[5]	Compare Fluconazole and amphotericin B for treating candidemia Studies comparing fluconazole with the combination of amphotericin B and 5-fluorocytosine, and studies of episodes of candidaemia that received sequential therapy with two agents	Adults with candidemia. 51 - 70% non C albicans Prospective open randomised controlled studies (3), prospective observational studies (2) and matched-paired cohort studies (1). A total of 862 patients	OR for amphotericin B versus Fluconazole total mortality - 1.06 (95% CI: 0.89, 1.20) and 1.08 (95% CI: 0.94, 1.24) based 3 RCTs and all 6 studies, respectively. candida-specific mortality - 1.00 (95% CI: 0.70, 1.45) and 0.90 (95% CI: 0.66, 1.96) for the 3 RCTs and all studies, respectively. clinical response - 1.14 (95% CI: 0.93, 1.39) and 1.09 (95% CI: 0.91, 1.31) for the 3 RCTs and all studies, respectively. microbiological failure - 0.99 (95% CI: 0.78, 1.26) and 1.03 (95% CI: 0.86, 1.23) for the 3 RCTs and all studies, respectively. No statistically-significant difference in eradication according to Candida species. However, a trend favouring amphotericin B was seen Toxicity - fluconazole had reduced drug-related toxicity (random-effects OR 2.95, 95% CI: 2.24, 3.89) based on data from all 6 studies. Renal toxicity was significantly more with amphotericin B (random-effects OR 3.20, 95% CI: 1.61, 5.01).
Girois, SB 2005[6]	Adverse effects of therapy for invasive fungal infections The included studies used intravenous conventional amphotericin B (AmB), amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), liposomal amphotericin B (L-AmB), and intravenous or oral itraconazole or fluconazole.	Participants had a variety of underlyin diseases Infants and neonates excluded 54 studies were included (n=9,228) i.e. 21 RCTs (n=3,721), 16 prospective cohort studies (n=2,153), 11 retrospective cohort studies (n=3,269), 3 case-control studies (n=96) and 3 case series (n=46).	Fever was less commonly associated with fluconazole than AmB (4 homogeneous studies). Nausea with or without vomiting was most common with itraconazole (mean 19.7%, range: 6 to 24). There was no difference in nausea between fluconazole and AmB (2 studies) or between L-AmB and conventional AmB (2 studies). Bronchospasm or cough without dyspnoea or hypoxia was more common with itraconazole (9.4%; n=233) and ABLC (8.5%; n=307) than with AmB (7.2%; n=1073). The meta-analysis showed no difference in rash between fluconazole and AmB (3 RCTs). Discontinuation of the study drug due to transfusion-related reaction was twice as common with ABCD (3.9%) and ABLC (3.7%) than with conventional AmB (1.4%). L-AMB was the least nephrotoxic of the lipid- soluble formulations (15%; n=797)

	Purpose	Studies	Outcome
			and AmB was the most nephrotoxic (33.2%, 95% CI: 30.7, 36). The meta-analysis showed that L-AmB was less nephrotoxic than conventional therapy; the OR (3 RCTs) was 0.40 (95% CI: 0.30, 0.54). No studies reported discontinuation of the study drugs due to hypokalaemia. One patient taking ABCD died of cardiac arrhythmia. Patients with underlying liver damage were excluded from itraconazole studies, but itraconazole was stopped in 1.6% due to hepatotoxicity (5 studies, n=442). Across other treatments, discontinuations due to hepatotoxicity ranged from 0.2% with AmB to 1.1% with ABLC. The meta-analysis showed no difference in hepatotoxicity between L-AmB and AmB (based on 2 RCTs in neutropoenic patients).
Crawford,F 2002[7]	Efficacy of oral treatments for dermatophyte infections of toe nail Included studies compared the following agents with each other and/or placebo: itraconazole (100 to 400 mg/day), terbinafine (250 to 500 mg/day), griseofulvin (500 to 1,000 mg/day), ketoconazole (200 mg/day) and fluconazole (150 to 450 mg/day). Studies used intermittent or continuous regimens of itraconazole. The duration of treatment ranged from 12 w to 18 m.	Most common isolate was T. rubrum 32 RCTs	3 RCTs (433 patients) of itraconazole versus placebo - itraconazole increased the cure rates at 12 weeks. 3 RCTs (337 patients) of terbinafine versus placebo- terbinafine increased the cure rates at 12 weeks. 2 RCTs (501 patients) of itraconazole versus terbinafine - terbinafine significantly increased cure rate at 11 and 12 months' follow-up after 3 months of treatment. The RD was -0.23 (95% CI: -0.15, -0.32) and the NNT was 5 (95% CI: 4, 8). <u>Different regimens of itraconazole and terbinafine</u> 2 RCTs (481 patients) - higher and prolonged dosages did not increase the cure rates. One RCT (47 patients) - no significant difference between continuous and intermittent terbinafine; cure rates 79 and 74%, 2 RCT (185 patients) - no significant difference between continuous and intermittent itraconazole . One RCT (50 patients) - no significant difference in the cure rates at 24 weeks between intermittent itraconazole for 3 compared with 4 months (64 versus 72%). 3 RCTs (188 patients)- no significant difference in the cure rates between griseofulvin (500 mg to 990 mg/day) and itraconazole (100 mg/day). All 3 trials found low cure rates. 3 RCTs - terbinafine (250 mg/day) increased cure rates in comparison with

	Purpose	Studies	Outcome
			griseofulvin (500 to 1,000 mg/day). 2 RCTs found no difference between griseofulvin (500 and 1,000 mg) and ketoconazole (200 mg). Dose and duration of fluconazole treatment. One RCT - 4 m (34%) treatment worse than 9 m (61%). One RCT- 450 mg fluconazole better than 150 and 300 mg One RCT - 450 mg fluconazole for 9 m better than 4 or 6 m therapy or placebo. One RCT - 250 mg terbinafine for 16 w better than 12 weeks treatment or intermittent 400 mg itraconazole. Adverse events (31 RCTs). - no significant difference in adverse events between active treatment with itraconazole, terbinafine or fluconazole and placebo.

Table 5 Some clinical trials on invasive fungal infections including cryptococcal infections in HIV

Chotmongkol V,2005[8]	treatment of cryptococcal meningitis in AIDS open- randomized, controlled, prospective clinical trial	1. amphotericin B (0.7 mg/kg/d) plus rifampin (600 mg/d) 2. amphotericin B (0.7 mg/kg/d) for 2 weeks, both followed by fluconazole (400 mg/ d) for 8 weeks 20 patients in each group	No significant differences between the groups in regard to a negative CSF culture at 2 and 10 w time until normal body temperature, number of deaths, and persistence of high CSF pressure after completion of treatment.
Brouwer AE, 2004 Thailand[9]	First episode of HIV-associated cryptococcal meningitis, randomised. serial quantitative CSF cultures on days 3, 7, and 14 of treatment.	1. amphotericin B (0.7 mg/kg daily) 2. amphotericin B plus flucytosine (100 mg/kg daily) 3. amphotericin B plus fluconazole (400 mg daily) 4.amphotericin B, flucytosine, and fluconazole. 64 patients	Cryptococcal clearance was significantly faster with amphotericin B plus flucytosine than with amphotericin B alone (p=0.0006), amphotericin B plus fluconazole (p=0.02), or triple therapy (p=0.02).
Mootsikapun P, 2003 Thailand[10]	HIV infected patients with primary cryptococcal meningitis, who had been treated initially with amphotericin B for 2 weeks randomized	1.fluconazole 600 mg daily (19) 2.itraconazole 600 mg daily (16) For 10 weeks	all patients recovered clinically. Culture negative rate for fluconazole group and itraconazole group were 100 and 94%. Difference not significant

Villanueva A, 2002[11]	Candida esophagitis double-blind randomized trial. Data were analyzed with a modified ITT 87% had HIV infection, median CD4 count -30 cells/mm. Candida albicans was the predominant isolate.	1.caspofungin (50 mg) (81) 2. fluconazole (200 mg) (94) intravenously once daily for 7 to 21 days	Favorable response rates in 81% on caspofungin and i85% on fluconazole Symptoms resolved in >50% in both groups by the fifth day. No patient in the caspofungin group developed serious drug-related adverse event; therapy was discontinued in one patient receiving fluconazole due to adverse effect. 4 w after stopping drug, symptoms recurred in 18 (28%) of 64 patients given caspofungin and in 12 (17%) of 72 patients given fluconazole (P = 0.19).
Smith, DE 2001[12]	Prophylaxis for systemic or deep fungal infections in HIV pos with CD4 counts < 300 cells double-blind, placebo-controlled, phase III trial ITT	1. itraconazole (200 mg per day) (187) 2. placebo (187) followed for 2 years.	Time to development of deep fungal infection did not differ between groups Itraconazole treatment significantly reduced the incidence of oral candidosis (25% vs. 48% P < 0.001) and time to development of oral candidosis (508 vs. 413 days, P < 0.001) but not the number of deep fungal infections (11 vs. 13). Survival did not differ significantly between groups (nine vs. 14 deaths). CD4 counts decreased significantly over time in both study arms. Adverse events did not differ between groups; 20% vs. 23% stopped study medication due to an adverse experience.
Rich, P 2001[13]	safety and efficacy of oral terbinafine for the treatment of tinea corporis or tinea cruris in those aged 18 to 75 years, with HIV infection (6) or diabetes (8), prospective, randomized, open-label studies in general community and referral centers.	Patients received oral terbinafine 250 mg once daily for 1 or 2 weeks.	Efficacy results were similar in both groups. All HIV-positive and 83% of diabetic subjects achieved mycological cure at week 6 based on culture results. There were no adverse events

Smith S, 2001[14]	Prospective, open-label, multicenter, randomized study for evaluating efficacy and safety of oral terbinafine for tinea pedis in patients who are HIV positive.	Twenty-seven patients were randomized to receive oral terbinafine 250 mg once daily for 2 or 4 weeks	Clinical cure in 82% Culture negativity 65% Terbinafine well tolerated
Saag, MS 1999[15]	Maintenance therapy for AIDS-associated cryptococcal meningitis. HIV-infected patients who had been successfully treated for a first episode of cryptococcal meningitis. Randomised	1.fluconazole or 2.itraconazole, both at 200 mg/d, for 12 months	The study was stopped prematurely on the recommendation of an independent Data Safety and Monitoring Board.13 (23%) of 57 itraconazole recipients had experienced culture-positive relapse, compared with 2 relapses (4%) noted among 51 fluconazole recipients (P = .006). The factor best associated with relapse was the patient having not received flucytosine during the initial 2 weeks of primary treatment for cryptococcal disease(relative risk = 5.88; 95% confidence interval, 1.27-27.14; P = .04).

1. Pienaar, E.D., T. Young and H. Holmes, *Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children.* Cochrane Database of Systematic Reviews, Issue 3. CD003940., 2006.
2. Clerihew, L. and W. McGuire, *Systemic antifungal drugs for invasive fungal infection in preterm infants.* Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003953., 2004.
3. McGuire, W., L. Clerihew and N. Austin, *Prophylactic intravenous antifungal agents to prevent mortality and morbidity in very low birth weight infants.* Cochrane Database of Systematic Reviews Issue 1. Art. No.: CD003850, 2004.
4. Chang, L.W., W.T. Phipps, G.E. Kennedy and G.W. Rutherford, *Antifungal interventions for the primary prevention of cryptococcal disease in adults with HIV.* Cochrane Database of Systematic Reviews, 2005(3. CD004773).
5. Kontoyiannis, D.P., G.P. Bodey and C.S. Mantzoros, *Fluconazole vs. amphotericin B for the management of candidaemia in adults: a meta-analysis.* Mycoses, 2001. **44**(5): p. 125-35.
6. Girois, S.B., F. Chapuis, E. Decullier and B.G. Revol, *Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis.* Eur J Clin Microbiol Infect Dis, 2005. **24**(2): p. 119-30.
7. Crawford, F., P. Young, C. Godfrey, S.E. Bell-Syer, R. Hart, E. Brunt and I. Russell, *Oral treatments for toenail onychomycosis: a systematic review.* Arch Dermatol, 2002. **138**(6): p. 811-6.
8. Chotmongkol, V., A. Arayawichanont, K. Sawanyawisuth and Y. Thavornpitak, *Initial treatment of cryptococcal meningitis in AIDS.* Southeast Asian J Trop Med Public Health, 2005. **36**(1): p. 170-3.

9. Brouwer, A.E., A. Rajanuwong, W. Chierakul, G.E. Griffin, R.A. Larsen, N.J. White and T.S. Harrison, *Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial.* Lancet, 2004. **363**(9423): p. 1764-7.
10. Mootsikapun, P., P. Chetchotisakd, S. Anunnatsiri and K. Choksawadphinyo, *The efficacy of fluconazole 600 mg/day versus itraconazole 600 mg/day as consolidation therapy of cryptococcal meningitis in AIDS patients.* J Med Assoc Thai, 2003. **86**(4): p. 293-8.
11. Villanueva, A., E. Gotuzzo, E.G. Arathoon, L.M. Noriega, N.A. Kartsonis, R.J. Lupinacci, J.M. Smietana, M.J. DiNubile and C.A. Sable, *A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis.* Am J Med, 2002. **113**(4): p. 294-9.
12. Smith, D.E., J. Bell, M. Johnson, M. Youle, B. Gazzard, S. Tchamouroff, G. Frechette, W. Schlech, S. Miller, D. Spencer, W. Seifert, M. Peeters, and K. De Beule, *A randomized, double-blind, placebo-controlled study of itraconazole capsules for the prevention of deep fungal infections in immunodeficient patients with HIV infection.* HIV Med, 2001. **2**(2): p. 78-83.
13. Rich, P., K.R. Houpt, A. LaMarca, K.H. Loven, T.C. Marbury, R. Matheson, B. Miller, S. Smith and J. Wolf, *Safety and efficacy of short-duration oral terbinafine for the treatment of tinea corporis or tinea cruris in subjects with HIV infection or diabetes.* Cutis, 2001. **68**(1 Suppl): p. 15-22.
14. Smith, S., K. Houpt, P. Rich, A. LaMarca, J.M. Weinberg, T.S. Alferez, E. Atillasoy and C. Opper, *Short-duration oral terbinafine for the treatment of tinea pedis in HIV-positive patients.* Cutis, 2001. **68**(1 Suppl): p. 30-9.
15. Saag, M.S., G.A. Cloud, J.R. Graybill, J.D. Sobel, C.U. Tuazon, P.C. Johnson, W.J. Fessel, B.L. Moskovitz, B. Wiesinger, D. Cosmatos, L. Riser, C. Thomas, R. Hafner, and W.E. Dismukes, *A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group.* Clin Infect Dis, 1999. **28**(2): p. 291-6.